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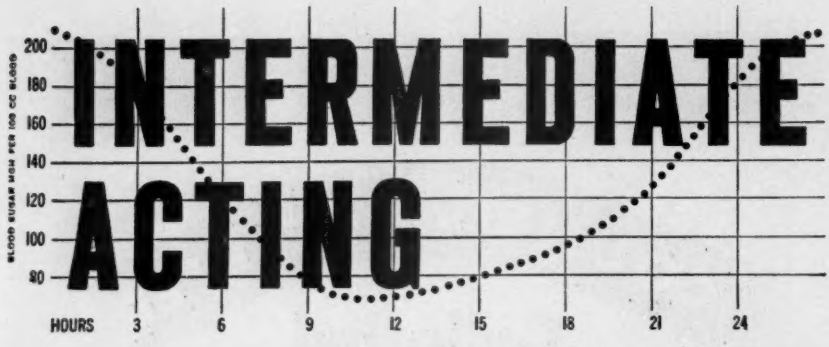
1. Gastroenterology (Oct.) 1951.
2. N.Y. State J. Med. (Aug.) 1951.
3. Editorial J.A.M.A. (Apr. 14) 1951.
4. Proc. Soc. Exper. Biol. & Med. (Oct.) 1951.



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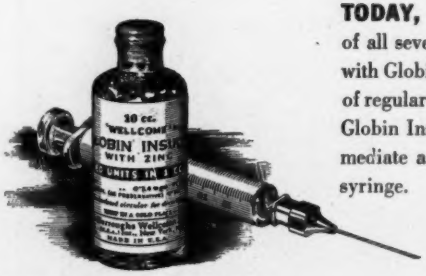

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1. Rohr, J.H., and Colwell, A.R.: Arch. Int. Med. 82:54, 1948.
2. Ibid Proc. Am. Diabetes Assn. 8:37, 1948

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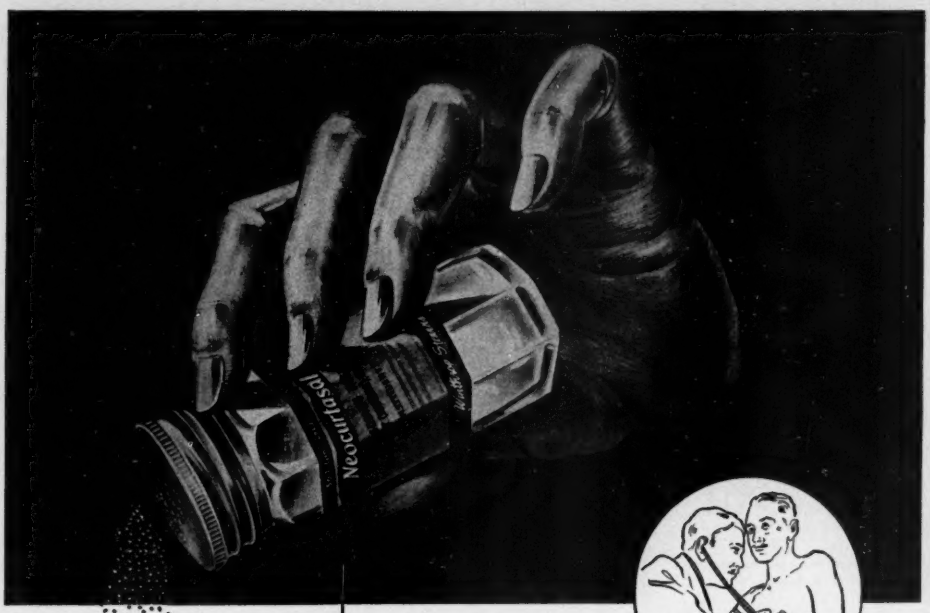

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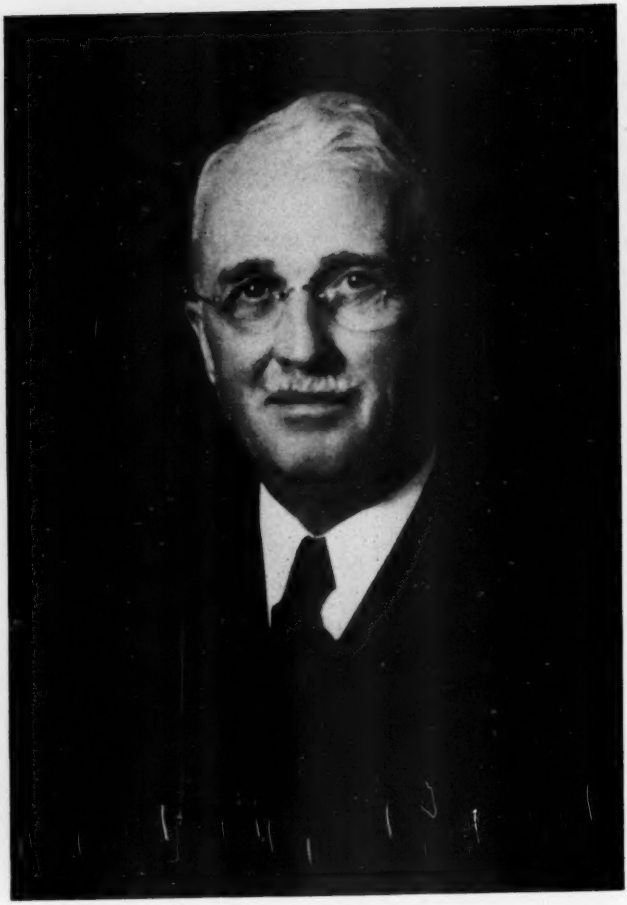

DR. N. C. GILBERT

DR. N. C. GILBERT

On Jan. 1, 1950, Dr. N. C. Gilbert retired as Chief Editor of the ARCHIVES OF INTERNAL MEDICINE. He headed the editorial board from 1932 to 1937, at which time he was officially appointed Chief Editor. During this period the ARCHIVES has experienced a healthy growth, as evidenced by a doubled circulation. Keen scientific judgment and absolute fairness marked his supervision of the ARCHIVES. His colleagues on the Editorial Board and at the American Medical Association offices will miss also his constant enthusiam and gentle, salty humor. Through the busy years, he has managed an active private and consulting practice; administered the affairs of the Department of Medicine of Northwestern University Medical School as its chairman; acted as chairman of the Medical Department at St. Luke's Hospital in Chicago and, with the help of numerous younger colleagues, made notable original contributions to the knowledge of coronary circulation and the management of coronary heart disease.

As he relinquishes his duties with the ARCHIVES and at Northwestern University Medical School, his friends take satisfaction in the soundness of his body and mind and wish him well in the pleasures and enterprises that lie ahead.

DR. ARTHUR BLOOMFIELD
DR. REGINALD FITZ
DR. RUSSELL M. WILDER
DR. GEORGE E. BURCH
DR. PAUL S. RHOADS, Chief Editor

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EFFECTS OF DELTA 5 PREGNENOLONE IN RHEUMATOID ARTHRITIS

ROLAND DAVISON, M.D.

PETER KOETS, Ph.D.

WILLARD G. SNOW, M.D.

SAN FRANCISCO

AND

CAPTAIN LYMAN G. GABRIELSON

MEDICAL CORPS, UNITED STATES ARMY

PREGNENOLONE (Δ^5-pregnen-3 β-ol-20-one, melting point 190C.) was first obtained synthetically from stigmasterol by oxidation of the C20 side chain [1] and subsequently from cholesterol by the same method.[2] It has been isolated in small amounts from hog testes,[3] but its isolation from human sources has not been reported.

Its relation to the physiologically important steroids in chemical structure and in pharmacologic properties has given rise to speculations about its possible role in the human organism as an intermediate substance in the synthesis and metabolism of these steroids.[4]

While chemically it can be regarded as a direct oxidation product of cholesterol, it can, in turn, be transformed to dehydroisoandrosterone

From the Departments of Medicine and Obstetrics and Gynecology, Stanford University School of Medicine, and the Letterman General Hospital.

This investigation was supported in part by grants from Stanford University Fluid Research Fund, the United States Public Health Service and the Schering Corporation.

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3. Ruzicka, L., and Frelog, V.: Testicular Extracts: I. Lipoids of Hog Testes, Helvet. Chim. acta **26**:975-994, 1943. Haines, W. J.; Johnson, R. H.; Goodwin, M. P., and Kuizenga, M. H.: Biochemical Studies on Hog Testicular Extract: I. Isolation and Identification of 5-Pregnen-3 (β)-oL-20-one, J. Biol. Chem. **174**:925-927 (July) 1948.

4. Butenandt, A.: On the Material Characterization of the Hormones of the Reproductive Glands: Their Constitution and Synthesis, Deutsche med. Wchnschr. **61**:823 (May 24) 1935.

by oxidation at C17, to progesterone by oxidation at C3 and to desoxycorticosterone by oxidation at both C3 and C21 (fig. 1).[5]

The resting adrenal cortex is rich in cholesterol esters, which are depleted when the experimental animal is subjected to stress or when the adrenal cortex is stimulated by injection of adrenocorticotropic hormone.[6] There is therefore good evidence that cholesterol is utilized in the synthesis of the steroid hormones, and the pathway of this synthesis may well be through pregnenolone.

Pharmacologically it displays to some extent all the hormonal activities common to the naturally occurring steroids, as shown in animal experiments. It was used extensively by Hoagland[7] and by Pincus[8] to reduce increased ketosteroid excretion which occurs as the result of

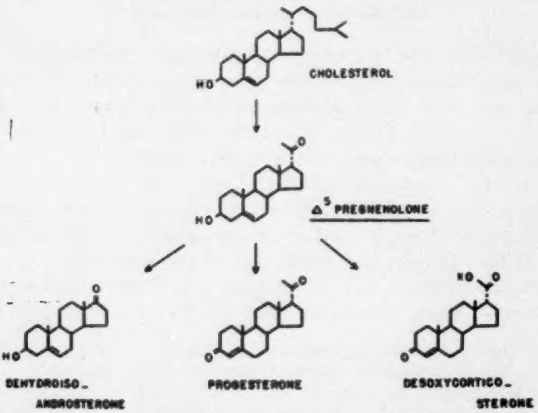

Fig. 1.—Relation of pregnenolone to cholesterol, dehydroisoandrosterone, progesterone and desoxycorticosterone.

stress in aviators. Simultaneously with the reduction of the ketosteroid excretion, the psychomotor performance improved. Hoagland postulated that its administration creates an optimum steroid balance, though the mechanism of conversion is obscure. While these observations were

5. Selye, H.: Textbook of Endocrinology, Montreal, Canada, Université de Montréal, 1947.

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made on essentially healthy persons, pregnenolone will also reduce the excessive ketosteroid excretion of pathologic origin which occurs in virilism in women.[9]

It appears to be free from toxic effects in man when administered in relatively large doses. Carbohydrate and electrolyte metabolism are unaltered even with prolonged administration, and no effect on renal clearances was observed by Abels and his associates.[10]

The possibility of some disturbance in steroid hormone metabolism in rheumatoid arthritis prompted studies of ketosteroid excretion by some of us. Urinary 17-ketosteroid excretion provides an index of adrenocortical activity. The 17-ketosteroids are derived from androgen precursors, two thirds of which in the male and, for practical purposes, all the androgen secreted by the female are derived from the adrenal cortex.

In most chronic debilitating diseases, ketosteroid excretion is low. We have confirmed the low excretion rates reported by others[11] in rheumatoid arthritis (additional observations are reported in this paper), though stress of various kinds increases adrenocortical activity and 17-ketosteroid excretion.[12]

Our observations of increased ketosteroid excretion in both male and female patients suffering from ankylosing spondylarthritis[13] indicate that an altered physiologic response common to the two sexes is responsible for the observed increase in ketosteroid excretion.

How and where ketosteroid precursors are degraded is unknown. Increased adrenocortical activity could account for the observed increase. It might result from a change in the material brought to the adrenal

9. Koets, P.: Unpublished observations.

10. Dean, A. L.; Abels, J. C., and Taylor, H. C.: Effects of Certain Hormones on Renal Function of Man, J. Urol. **53**:647-653 (May) 1945. Abels, J. C.; Young, N. F.; Taylor, H. C., Jr., and Rhoads, C. P.: The Effects of Testosterone, Testosterone Propionate and Pregnenolone on Protein Fabrication in Man, Endocrinology **35**:213 (Sept.) 1944.

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13. Davison, R. A.; Koets, P., and Kuzell, W. C.: Excretion of 17-Ketosteroids in Ankylosing Spondylarthritis: A Preliminary Report, J. Clin. Endocrinol. **7**:201-204 (March) 1947; Effect of Roentgenotherapy on Urinary 17-Ketosteroid Excretion in Ankylosing Spondylarthritis, ibid. **9**:79-88 (Jan.) 1949.

gland or from failure of some mechanism whereby these precursors are converted to substances other than 17-ketosteroids.

Diminished ketosteroid excretion observed in rheumatoid arthritis does not necessarily indicate loss of adrenocortical reserve.[14]

The ability of pregnenolone to reduce 17-ketosteroid excretion and the possibility of readily converting it to other steroids which the individual might utilize to its advantage prompted us to study the effects of its administration in ankylosing spondylarthritis, the objective being (1) to determine whether pregnenolone would reduce the high rate of ketosteroid excretion which occurs in the disease and (2) to determine what effect the steroid might have on symptoms and course of the disease. A preliminary report of the results in a few cases was presented to the Lane Hospital Medical Society April 15, 1949. The remarkable clinical improvement observed in these patients prompted trial of pregnenolone in other rheumatic diseases.

Intramuscular injections of pregnenolone have been given to 30 patients. Twelve of these patients, 8 males and 4 females, have typical ankylosing spondylarthritis; 13 patients have rheumatoid arthritis; 1 has rheumatoid arthritis with spondylarthritis and degenerative joint disease; 1, rheumatoid arthritis complicated by glomerulonephritis (this case may be early disseminated lupus), and 1, rheumatoid arthritis with psoriasis.

The material used in the investigation was provided by the Schering Corporation, through Edward Henderson, M. D., its director of clinical research. For the initial experiments pregnenolone acetate in sesame oil, 50 mg. per milliliter, in 10 ml. rubber-capped vials, was supplied. Subsequently an aqueous suspension of crystalline pregnenolone (100 mg. per milliliter) was tried. Use of this material was discontinued because injection of it was difficult. More recently pregnenolone acetate in 80 per cent sesame oil and 20 per cent benzyl benzoate (50 mg. per milliliter) and an aqueous suspension of pregnenolone (50 mg. per milliliter) have been used.

All the patients were hospitalized for initial studies, and some were hospitalized for the entire period of investigation. A few were given pregnenolone as ambulatory outpatients. Most laboratory examinations were made in the clinical laboratories of Stanford University Hospitals and Letterman General Hospital. A few were made in the laboratory of the senior author, using standard procedures. All sedimentation rates recorded are Wintrobe estimations. All ketosteroid determinations were made in the steroid laboratory of the Stanford University Medical School, using the method previously described.[13] None of the patients were on strict dietary control, and balance studies were not made.

14. Thorn, G. W., and others: Studies on the Relation of Pituitary-Adrenal Function to Rheumatic Diseases, New England J. Med. **241**:529-537 (Oct. 6) 1949.

Every effort was made to keep the investigation as objective as possible. Patients were checked by disinterested observers.

The patients were told that the injections were a new treatment which might help or might not. Placebos were given without knowledge of the patients when the change was made, nor did they know when pregnenolone was again given them. Dosage schedules have been varied from 50 to 300 mg. a day. When pregnenolone acetate was used, 100 mg. was given at a single injection, and when the dosage was increased to 200 mg. two injections were given each day. Pregnenolone aqueous suspension in the later experiments has been given in two daily injections of 150 mg. each.

Warming of the vials has been necessary to secure solution of the crystals when the acetate in oil was used; otherwise, the oil preparation shows undissolved crystals. The injection of the cold material occasionally has caused pain in women; such pain did not occur in the males. When the vials were warmed and the material then injected, no pain occurred. When aqueous suspension was given, some of the patients experienced a prickling or stinging sensation at the site of injection for five to ten minutes after injection.

In table 1 are summarized the results in 5 cases of rheumatoid arthritis involving only joints of the extremities, 5 cases of spondylarthritis, 1 case of rheumatoid arthritis involving joints of the extremities superimposed on old spondylarthritis and degeneration of the joints and 1 case of rheumatoid arthritis complicated by glomerulonephritis. The case histories of these patients are appended. Some of these patients continue to receive injections of pregnenolone at the time this paper is written.

In most cases, the pattern of response is the same. In spondylarthritis, ketosteroid excretion is reduced in a few days, accompanied with increased mobility of the spine in cases in which fixation was due to spasm, not ankylosis. Pain and spasm were greatly diminished, and in patients with diminished chest expansion it increased. In those patients having rheumatoid arthritis involving joints of the extremities, usually within a week and sometimes within three or four days there was relief of stiffness and pain, great improvement in muscle strength and loss of fatigue, which was replaced by a feeling of well-being.

Appetite was frequently but not invariably improved. In those patients with anemia the blood picture improved rapidly. Reduction in joint swelling, particularly in those cases with large joint effusions, came more slowly. Reduction in sedimentation rates did not parallel clinical improvement but came later.

No evidences of toxicity have been observed from prolonged administration of pregnenolone. There has been no elevation of the fasting blood sugar and no edema. There has been no effect on the menstrual

TABLE 1.—*Summary of Cases*

Case	Age	Sex	Diagnosis	Duration, Yr.	Severity	Pregnenolone Dosage,* Mg./24 Hr.	Duration, Days	Improvement First Noted	Complete Absence of Symptoms and Objective Findings	Clinical Notes
1	21	M	Rheumatoid arthritis	..	Moderate	Aqueous 100	21	None	In 16 days	Symptoms and signs recurred in one week after use of steroid was stopped
						Acetate 100	16	At 4 days —		
						Acetate 100 every other day	55			
2	22	M	Rheumatoid arthritis	2/12	Moderate	Acetate 100	14	At 4 days	In 14 days	No recurrence of active disease since use of drug was discontinued
						Placebo	7		Recurrence in 6 days	
						Acetate 200	16	4th day symptom-free		
						100	5			
						Placebo	4	Symptoms recurred	Recurrence in 1 day	
						Acetate 100	30	Symptom free at 3 days	3 days	
3	46	F	Rheumatoid arthritis	10	Severe	Acetate 100	14	At 3 days	No pain or stiffness Improved mobility, muscle strength in 14 days	Severe joint destruction, deformities, bone atrophy and anemia; when pregnenolone was discontinued after 30 days, joint pain and swelling recurred in 4 days
						Aqueous 300	Continuing			
4	21	M	Rheumatoid arthritis	1	Moderate	Acetate 200	Continuing	At 3 days	Asymptomatic; disappearance of objective signs in 3 days	First objective evidence decreased swelling at 5 days
5	27	M	Spondylarthritis	?	Moderate	Acetate 200	14	At 3 days	Asymptomatic in 3 weeks	Still receiving treatment
						Aqueous 300	7			
6	32	F	Rheumatoid arthritis	1/12	Very acute	Acetate 200	7	At 3 days	In 36 days	Recurring activity in 2 days when use of pregnenolone was stopped at end of first month
					Severe	Acetate 100	75			
7	37	F	Spondylarthritis	4	Mild	Acetate 100	30	At 16 days	In 23 days	Moderate euphoria; much premenstrual pain and involuntary muscle spasm before use of pregnenolone was begun; menstruation improved; initial 17-ketosteroid excretion 26.7 mg. a day
						Aqueous 100	30			
8	23	M	Spondylarthritis	4	Severe	Acetate 100	9	At 3 days	In 30 days	Return of findings and symptoms on placebo; slower response to second course; symptomless in 60 days
						Placebo	8			
						Acetate 100	38			
9	54	M	Rheumatoid arthritis; spondylarthritis; joint degeneration	10/12	Severe with fever	Aqueous 200	14	None	After 10 days on 200 mg. of acetate	Slight improvement with 100 mg. of acetate a day; rapid subsidence of pain; absorption of fluid from knee with 150 mg. a day; still symptom free 1 month after discontinuance of therapy
						Acetate 100	14	At 7 days		
						Acetate 150	35			
						Acetate 100	21			
10	19	F	Spondylarthritis	6/12	Severe	Acetate 100	7	At 7 days		From high sedimentation rate; leukocytosis at onset; recurrence of symptoms when use of drug was discontinued at 5 weeks; improvement when drug was reinstated.
						Aqueous 100	7			
						200	21			
11	28	M	Advanced spondylarthritis	3	Severe	Acetate 100	35	None	No improvement	Previous roentgen therapy failed
						200	30	None		
12	29	F	Rheumatoid arthritis; glomerulonephritis	2	Severe	Acetate 200	12	6 days	Still uncontrolled	Effusion in knee persisted
						Placebo	6	Recurrence in 3 days		
						Aqueous 150-300	14	No improvement		

* "Aqueous" refers to aqueous suspension of crystalline pregnenolone; "acetate" refers to pregnenolone acetate in sesame oil or 80 per cent sesame oil and 20 per cent benzyl benzoate.

cycle, the duration of menstruation or its character in any of the women who have received it. Pregnenolone is a known stimulant to spermatogenesis; though sperm counts have not been made, none of the men has had diminished potency. One man (case 9) who had lost sexual potency recovered it while he was under treatment, probably as a result of control of the disease and improvement in general strength.

The euphoria observed by Hench [15] following large doses of 17-hydroxy-11-dehydrocorticosterone is not seen in patients receiving pregnenolone. One patient did become exhilarated and had difficulty sleeping on a daily dosage of 300 mg. of the pregnenolone aqueous suspension.

When use of pregnenolone is discontinued after short term administration, symptoms and signs of active arthritis recur in a few days. One patient (case 1) who received pregnenolone daily for thirty-seven days and then was given 100 mg. of pregnenolone acetate every two days for two months continued to show no evidence of arthritis; five days after discontinuance of its use pain and joint swelling recurred.

Comment on the 18 additional patients who have received pregnenolone but are not reported in detail in this paper deserve mention. There were 4 men and 2 women with spondylarthritis. Two of the men who had great clinical improvement from 100 mg. of pregnenolone daily for three and four weeks respectively were lost by transfer to other hospitals. One man with complete ankylosis of the spine and little residual active disease showed no perceptible change from 50 mg. of pregnenolone acetate daily over a two week period and refused further trial of the steroid. One woman with ankylosing spondylarthritis had a complicating psychosis. She appeared greatly improved in two weeks, but evaluation was unsatisfactory because of the psychosis. One woman with psoriasis and rheumatoid arthritis failed to show symptomatic or objective improvement from daily injection of 100 mg. doses of aqueous suspension for two weeks, and refused further injections.

One 34 year old man with severe gouty arthritis was given 200 mg. of pregnenolone acetate for six and one-half days without benefit. The same patient was given 100 mg. of pituitary adrenocorticotropic hormone (ACTH) divided into six doses at six hour intervals, also without symptomatic or objective improvement, although the ACTH increased excretion of uric acid.

One young woman with a diagnosis of disseminated lupus was given 300 mg. of pregnenolone aqueous suspension daily for two weeks. The

15. Hench, P. S.; Kendall, E. C.; Slocumb, C. H., and Polley, H. F.: The Effect of a Hormone of the Adrenal Cortex (17-Hydroxy-11-Dehydrocorticosterone: Compound E) and of Pituitary Adrenocorticotropic Hormone on Rheumatoid Arthritis: Preliminary Report, Proc. Staff Meet., Mayo Clin. **24**:181-197 (April 13) 1949.

articular symptoms were slightly improved and the swelling was reduced, but she was so greatly emaciated and had so little muscle into which the material could be injected that injections were discontinued.

One 54 year old white woman has had long-continuing active rheumatoid arthritis resulting in much destruction and deformity of joints and known allergy to many drugs. Her obese buttocks made injections difficult, and many of them failed to deposit the oil solution in the muscle, resulting in large, hard, painful nodules necessitating discontinuance of treatment.

COMMENT

Though the intramuscular injection of pregnenolone appears to bring about remission of rheumatoid arthritis within a short time, its action in some cases is delayed as long as three or four weeks. Case 9 in the table is an example of this type of response. Patients with spondylarthritis with low urinary 17-ketosteroid excretion appear to respond more slowly, and 2 spondylarthritic patients (cases 11 and 13) who received what appeared to represent adequate dosage of pregnenolone failed to respond.

The recurrence of symptoms and objective evidence of activity within days after the hormone is discontinued appears to be good evidence that the steroid is responsible for the observed effects. Dosage and form of administration are important considerations. The results of injection of aqueous suspension of crystalline pregnenolone are much less effective than pregnenolone acetate in oil. No obvious effects were observed from daily administration of 50 mg. Many patients responded promptly to 100 mg. whereas others needed 200 mg. daily.

Experience to date indicates that the effective daily dose is 200 mg. A new preparation, which permits use of larger doses, is now being tried to determine whether more rapid control is possible without production of toxic effects. After symptoms have been relieved, reduction in dosage to 100 mg. daily appears sufficient to maintain the benefits; 100 mg. every second day may even be sufficient.

Nothing is known regarding the absorption of pregnenolone, and it appears probable from clinical observation that its administration in oil delays absorption to furnish a continuous supply of material for conversion to other steroids. Until some knowledge is obtained of its biosynthesis, it seems futile to conjecture how pregnenolone effects remissions in rheumatoid arthritis. Urinary metabolites may give some clue to possible conversions. Studies of these metabolites are now in progress.

Pregnenolone appears to be less rapidly effective than either 17-hydroxy-11-dehydrocorticosterone or the pituitary adrenocorticotropic hormone (ACTH). Unlike them, it appears to be free of the toxic effects which result from their administration over long periods.

Pregnenolone can be made readily at low expense, an important factor in long term administration, which appears necessary at the present time.

SUMMARY

The synthetic steroid Δ^5 pregnenolone, administered by intramuscular injection in adequate dosage, effects remission in rheumatoid arthritis. When it is withdrawn, symptoms and signs of active disease return, usually within a few days. No toxic effects have been demonstrated from daily injection over a four month period. Further studies are necessary to establish dosage schedules and determine its mode of action. This report is presented as a clinicoexperimental study.

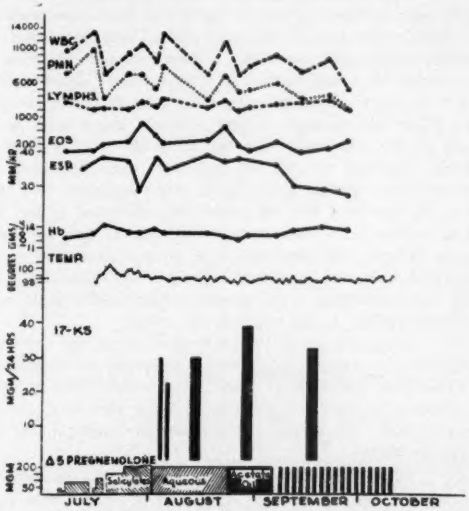

Fig. 2.—Laboratory data for case 1.

REPORT OF CASES

CASE 1.—B. R. B., a 21 year old white male sergeant was well until July 1, 1949, at which time he noted sudden onset of pain, swelling, redness and tenderness in the right wrist and hand. On the following day similar symptoms appeared in the left knee and left ankle. On July 6 he was admitted to the Station Hospital at Williams Air Force Base, Ariz. Physical examination revealed red, tender, warm swelling of the right wrist, right hand and left knee. The remainder of the physical examination disclosed essentially normal conditions. He was treated with salicylates, which produced relief of the pain but no objective improvement in the articular swelling. On July 16 he was transferred to Letterman General Hospital with a tentative diagnosis of acute rheumatic fever without cardiac involvement.

On the patient's entrance to Letterman General Hospital his right wrist, right hand and interphalangeal joints of the fingers of the right hand were swollen, tender, warm and red. There was marked swelling of the left ankle, with tenderness and slight swelling and stiffness of both knees. He was again given a salicylate, which gave some relief from pain, but the objective joint findings remained unchanged. An electrocardiogram taken on July 21 was entirely normal, the P. R. interval being 0.16 second. On July 23, a diagnosis of acute rheumatoid arthritis was made. Administration of salicylates was continued for one week, again with only moderate subjective improvement and no objective improvement. Physical examination on August 2 again revealed marked tenderness, swelling, redness and heat in the right wrist and right metacarpal joints and the interphalangeal joints of the fingers of the right hand. Both knees were warm and tender, and in the right knee fluid was present. Both ankles were warm, tender and swollen. On August 2, daily intramuscular injections of 100 mg. of pure pregnenolone in aqueous suspension were begun, and they were continued through August 23. During that period, the right wrist, both knees and both ankles remained swollen, warm, tender and red. No subjective or objective change was noted. On August 24 administration of pregnenolone acetate in sesame oil, 100 mg. daily, was begun. This was given daily through September 5.

On August 28 the patient began to feel definitely improved. He was allowed out of bed to be up in a wheelchair. Marked subjective relief of all of his involved joints was noted. Swelling, redness and tenderness were diminished. By August 31 he was up and about without a wheelchair and complained only of slight pain and stiffness in his left knee and left ankle. He continued to feel well, and by September 9 all swollen joints had returned to normal in that they had no tenderness, swelling or redness. He continued to be up and about, and on September 9 the dose of pregnenolone was reduced to 100 mg. every other day. This therapy was continued, and by October 7 the patient felt practically well; his only complaint was residual stiffness in the left knee and ankle.

On July 18 a roentgenogram of the chest revealed entirely normal conditions, and roentgenograms of the hands, wrists, ankles and knees showed no abnormalities. On August 17 the total protein level of the blood was 5.1 Gm. per hundred cubic centimeters (albumin 3.4 Gm. and globulin 1.7 Gm.; albumin-globulin ratio 2.0). The urine was normal. The antistreptolysin titer on August 3 was less than 100 units per cubic centimeter.

Case 2.—C. E. R., a 22 year old white male corporal, was well until he fractured a metatarsal bone in his left foot in August 1948. Since that time he noted occasional swelling and pain in this foot. On May 20, 1949 the left foot became noticeably swollen and tender. He was admitted to an Army hospital in Japan and was returned to the Zone of the Interior and admitted to Letterman General Hospital June 17, 1949, with a diagnosis of traumatic arthritis of the left foot. On June 26 the patient noted swelling and soreness in his left knee, and on July 12 the right wrist also became swollen and tender.

The patient had the usual childhood diseases without sequelae. Physical examination on his admission to Letterman General Hospital revealed nothing significant except that the left foot was slightly swollen and tender and the ankle was painful to all movement. On physical examination on July 26, the hands and feet were cold and wet, and there was slight swelling in the middle finger of the left hand and the second and third fingers of the right hand. There was pronounced atrophy of the interosseus and the extensor muscles of the arms, most evident on the right. The feet were dusky and swollen, the left more so than the right; the left metatarsal arch was exceedingly tender, and the left ankle was painful on all active and

passive movements and moderately swollen. The skin temperature of the left knee was increased, and the knee was moderately swollen; fluid was obviously present. The patient showed some pain on flexion of the knee. There was marked atrophy of the quadriceps group of the left leg. Measurement of the circumference of the knees showed the left to be 2 cm. larger at the upper border of the patella.

Repeated examinations of the urine showed normal conditions. Serologic tests on admission elicited a positive Kahn reaction, a positive Wassermann reaction and a quantitative Kahn reaction of 10 units. The spinal fluid was entirely normal. The blood uric acid level was 3.4 mg. per hundred cubic centimeters. Results of routine agglutination tests were all negative. A roentgenogram of the chest showed no abnormalities, and roentgenograms of the feet, ankles and knees revealed no pathologic conditions of bones or joints.

On admission to the hospital the patient complained only of slight pain and difficulty in walking on the left foot. A routine serologic test was reported as showing a positive reaction, but the patient stated that he had had no primary or secondary manifestations of syphilis. However, repeated serologic tests were

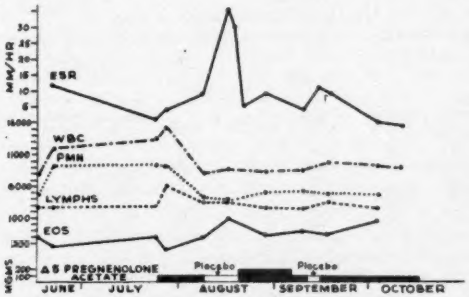

Fig. 3.—Laboratory data for case 2.

also reported as eliciting positive reactions; therefore penicillin therapy was started on July 15, 1949. He was given 100,000 units every three hours for a total dose of 10,000,000 units. On June 26 the patient first began to complain of swelling and soreness in his left knee. Two weeks later, his right wrist also became tender and swollen and a diagnosis of rheumatoid arthritis was made.

On July 26 administration of pregnenolone acetate in sesame oil, 100 mg. daily, was started. By August 5 the patient was subjectively and objectively improved and was up and about the ward, practically free of pain. The effusion in his knee and wrist had completely disappeared, and the redness, tenderness and swelling of all joints had disappeared.

On August 10 use of pregnenolone was discontinued, and sesame oil was given daily as a control without the patient's knowledge. By August 16 he was again complaining of pain and tenderness in his joints, and again there were swelling, redness and effusion into the left knee. On August 21 pregnenolone therapy was resumed (200 mg. daily), and by August 25 all evidence of joint involvement had again disappeared. This therapy was continued until September 7, when the dosage of pregnenolone was lowered to 100 mg. daily, and on September 12 he

again was given sesame oil without pregnenolone. By September 13 the articular condition had again flared up, and the patient was subjectively and objectively worse. Administration of pregnenolone was resumed on September 16 (100 mg. daily), and on the third day of treatment all joint involvement again cleared. This therapy was continued until October 17, when it was discontinued. During this period the patient remained entirely asymptomatic, and since use of pregnenolone has been stopped he has continued to do well.

The accompanying graph (fig. 3) shows blood changes, with reversal of sedimentation rates following injections of pregnenolene and increased sedimentation accompanying the recurrence of active disease when placebos were given.

Case 3.—A. L., a 46 year old white married woman, entered the Stanford University Hospital on Oct. 13, 1949 with a long history of progressive arthritis. In 1939 stiffness and tenderness of both knees developed, followed by swelling of her ankles and feet. Subsequently most of her joints became involved and she became more and more of an invalid. She had been treated with gold salts, vaccines of various kinds, neostigmine, vitamins, intravenous injections of procaine hydrochloride, physical therapy, removal of infectious foci, transfusions, etc., all

Table 2.—*Blood Counts in Case 3*

				Differential Count					
				Neutrophils					
	Hemoglobin, Gm./100 Cc.	Hematocrit, %	White Cells	Segmented	Band	Lymphocytes	Monocytes	Eosinophils	Sedimentation Rate, Mm./Hr.
10/14/49	11.3	34	2,700	42	4	22	4	24	..
10/17/49	12.8	..	4,100	53	11	15	..	18	..
10/20/49	....	..	5,000	52	8	16	..	19	..
10/25/49	13.4	39.5	4,200	56	2	20	..	20	..
11/ 5/49	....	42	5,500	54	..	24	..	22	..
11/14/49	15.0	41	7,200	44	16	20	..	20	32

with no lasting effect. For two years before entry she was taking at least two injections of either meperidine (demerol®) hydrochloride or methadone hydrochloride daily so that she could do a little housework without pain.

The past history was essentially noncontributory. Physical examination revealed a thin, crippled woman who walked with considerable difficulty, keeping her knees stiff and merely shuffling along. Both hands showed marked deformity, with ankylosis of many of the joints and subluxation of others. The movement of her wrists was seriously limited, and they were thickened. There was a 15 degree flexion deformity of the right elbow, with a loss of supination of the forearm. Abduction and rotation of the right shoulder were limited and painful. There was marked crepitation in the right hip which could be heard across the room when she walked, and flexion of the thigh on the trunk was limited to 150 degrees. Both knees were enlarged without fluid, and both ankles were thickened. Both feet were badly deformed. There was extreme muscular atrophy everywhere.

Roentgenograms of the feet revealed severe demineralization of the bones, and both hips showed marked arthritic changes with almost complete loss of joint space on the right. The urine was normal, and the twenty-four hour urinary excretion of 17-ketosteroids was 2.9 mg. The blood sugar level was 96 mg., the calcium level was 8.8 mg. and the phosphorus level 3.15 mg. per hundred cubic centimeters. Blood counts are shown in table 2.

On October 14 treatment was started with 100 mg. of pregnenolone acetate intramuscularly twice daily, and at the same time use of all narcotics was stopped, and simple empirin® compound (acetylsalicylic acid, acetophenetidin and caffeine) was given as needed for pain. On October 17 she stated that she was not so stiff, and on October 20 she said that she was having very little pain and that her muscular strength had increased a great deal. At that time she was able to turn herself over in bed for the first time in over eight years, walk to the bathroom unassisted and rise from the toilet without aid. On October 25 she had an urticarial reaction which was controlled with tripelennamine (pyribenzamine®) hydrochloride, 50 mg. three times a day. She was discharged from the hospital on October 29, to continue taking pregnenolone at home. She received 100 mg. in oil daily until November 1, and since then she has received two injections daily of 150 mg. of pregenolene in aqueous suspension until the time of writing. She continues free from pain and stiffness.

In summary, this 46 year old woman with advanced rheumatoid arthritis accompanied by moderately severe anemia, who received as her only treatment intramuscular pregnenolone for a period of thirty days, was rapidly relieved of pain and stiffness, gained muscular strength and recovered remarkably from the accompanying anemia.

CASE 4.—G. D. H., a 21 year old white male Army corporal was well until October 1948, when he began to have pain in the shoulders and hips. During the period from October 1948 to June 1949 he had recurrent pain, swelling and stiffness in both knees and ankles, and the toes of the right foot. During June the right knee and the toes of the right foot became more painful and swollen, and on June 30 he was hospitalized at the station hospital at Hamilton Field Air Force Base, Calif. Significant physical findings at the hospital were marked tenderness and swelling of the right knee and swelling and tenderness of the right great toe. Sedimentation rates were persistently elevated, varying from 15 to 40 mm. an hour. On August 1 the antisteptolysin titer was 166 units per cubic centimeter.

On October 10 the patient was transferred to Letterman General Hospital, at the time of transfer complaining only of pain in the joints of both feet. Both ankles were moderately swollen, tender to palpation and painful on any motion. There was no redness or increase in skin temperature over the painful joints. A diagnosis of rheumatoid arthritis was made.

After admission to the hospital the patient continued to complain of pain in both feet. On October 19 daily muscular injections of pregnenolone acetate in sesame oil (200 mg.) were started. By October 22 the patient noted a diminution of the articular pain, and by October 24 a marked decrease in the swelling was noted in the affected joints.

Laboratory Data.—On admission, the total white blood cell count was 7,550, and the hemoglobin content was 14.8 Gm. The sedimentation rate was 11 mm. in one hour. Results of urinalysis were normal: the antistreptolysis titer was 125 units per cubic centimeter. The urinary 17-ketosteroid excretion on October 9, 10 and 11 averaged 8.4 mg. daily; on October 13 12.3 mg., and on October 22, 23 and 24 averaged 13.7 mg. daily. A repeat white blood cell count on October 25 was 6,900 and the hemoglobin content 14.8 Gm. The sedimentation rate was 15 mm. in one hour.

Treatment was interrupted by the patient's transfer to another hospital.

CASE 5.—J. M. M., a 27 year old white male sergeant, was well until Aug. 25, 1949, at which time an infection of the upper respiratory tract developed with a severe sore throat. This occurred while the patient was aboard ship en route

from Hawaii to the United States. On August 31 he noted sudden weakness of both knees, and during the next two days both knees began to swell and become painful. On September 2 he was hospitalized at Camp Stoneman, Calif. On admission the temperature was 102.4 F., the white blood cell count 16,500 and the sedimentation rate 30 mm. in one hour. After salicylate therapy had been used for twenty-four hours, the temperature returned to normal. While the patient was in the hospital, the great toe on the right and the right foot became swollen, red and tender. Repeated electrocardiograms were normal.

On September 28 the patient was transferred to Letterman General Hospital. The only significant condition observed on physical examination was tenderness of the metatarsal arch of the right foot. There was no redness or swelling of any joint.

Course in the Hospital.—On September 30 the patient began to complain of pain low in the back, and this became progressively worse until it was difficult for him to walk, bend or be comfortable in any position. Roentgenograms showed sclerosis of both sacroiliac joints and arthritic changes in several apophysial joints. Salicylates failed to control the pain in the back. On October 19 daily intramuscular injections of pregnenolone acetate in sesame oil (200 mg.) was begun

TABLE 3.—*Blood Counts in Case 5*

	Hemoglobin, Gm./100 Cc.	White Cells	Differential Count				Sedimentation Rate Mm./Hr.	Packed Cell Volume
			Neutrophils, %	Lymphocytes, %	Monocytes, %	Eosinophils, %		
On admission.....	13.3	11,300	77	15	8	..	20	44
9/30/49.....	12.6	7,900	60	27	10	3	31	..
10/25/49.....	12.6	10,400	70	22	6	2	15	42
11/ 1/49.....	13.0	9,600	..	..	..	..	35	44
11/ 9/49.....	13.3	11,200	69	24	4	3	35	45
11/25/49.....	....	8,000	63	32	5	..	15	..

and continued until November 4, when aqueous suspension of pregnenolone, 300 mg. daily, was substituted. Improvement was noted by the patient on the third day of pregnenolone therapy, and he became asymptomatic by November 4. On admission, the results of urinalysis and of serologic tests were negative. On October 25, the blood uric acid level was 4.1 mg. per hundred cubic centimeters. Repeated electrocardiograms were normal. Administration of pregnenolone was discontinued November 11. The patient continued free of symptoms and physical signs until November 29, when he was discharged. No hematologic examination was made between November 9 and November 25, at which time the sedimentation rate was normal.

CASE 6.—M. R., a 32 year old white married woman was admitted to Letterman General Hospital on June 23, 1949. The patient was well until May 1949, at which time she had a flare-up of a mild dermatitis of her hands with purulent crusting lesions on the fingers. She was aboard ship en route to Okinawa, and the ship's doctor prescribed sulfadiazine and advised a sunbath. The following day, after she had taken a total of 4.5 Gm. of sulfadiazine over an eight hour period, a vesicular exfoliative dermatitis developed over the parts of her body which had not been protected by her bathing suit. On May 12 she was hospitalized on Guam, where she was acutely ill with an exfoliative dermatitis and had a septic fever up to 41.3 C. (106.3 F.). Signs and symptoms of a toxic encephalitis developed with delirium for seventeen days, papilledema, meningismus

and elevated spinal fluid protein. During this period a toxic hepatitis also developed, and the patient became clinically jaundiced. The liver was palpable 3 to 4 cm. below the costal margin; serum bilirubin rose to 15 mg. per hundred cubic centimeters, and a generalized anasarca developed with fluid in the abdomen and edema of the extremities. She also bled from the gastrointestinal and urinary tracts and had hemorrhages into the skin. Prothrombin activity was markedly lowered; bleeding and clotting times were prolonged. During the acute febrile course penicillin, aureomycin and streptomycin were tried without influence on the fever or general course. A mass became palpable in the left lower abdominal quadrant, measuring approximately 3 by 6 cm. The mass was freely movable and was thought to be located in the anterior abdominal wall.

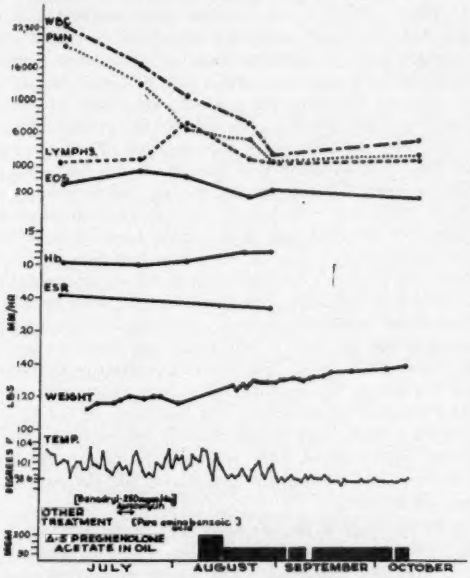

Fig. 4.—Laboratory data for case 6.

Laboratory studies done on Guam showed all routine agglutination tests to give negative reactions; the urine was normal except for a specific gravity which never rose above 1.015 and presence of red cells during the time of the hemorrhagic diathesis. Total leukocyte counts varied between 10,000 and 19,000 with a predominance of polymorphonuclear leukocytes and a persistent 3 to 6 per cent eosinophils. At no time was there leukopenia. Total serum proteins fell to 4 Gm. per hundred cubic centimeters, and the albumin-globulin ratio was reversed.

In 1944 the patient was treated with an unknown type of sulfonamide for an infection of the upper respiratory tract, and a rash developed while she was on this therapy. In June 1947 a mild scaling dermatitis developed on both hands which never completely cleared but was kept under control by conservative local treatments.

Physical examination when the patient was admitted to Letterman General Hospital revealed a white woman who appeared acutely ill. She weighed 133 pounds (60.3 Kg.). A scattered, erythematous, papular eruption was present over the face and extremities. There were no palpable lymph nodes. The lungs were clear. The blood pressure was 105 systolic and 65 diastolic. The heart was normal except for tachycardia (rate 100). The liver was palpable approximately 4 cm. below the right costal margin and was nontender. The spleen was not palpable. A smooth, firm, slightly tender, sausage-shaped mass was palpable in the left lower part of the abdomen. It seemed to be fixed to the rectus muscle. Pelvic and rectal examinations revealed nothing significant. There was marked generalized muscle atrophy.

During the first week of hospitalization the patient's temperature varied from 37.2 to 39.3 C. (99 to 102.7 F.) and the pulse rate from 98 to 120 per minute. She had profuse drenching night sweats and complained of generalized weakness. On July 3, administration of diphenhydramine hydrochloride (benadryl hydrochloride®) was begun in 50 mg. doses, with a total dosage of 250 mg. daily. The drug failed to influence the temperature, which still spiked as high as 39.5 C. 103.1 F.). On July 5 polyarthritis, with red, tender, swollen joints, developed. The left wrist, left knee and both ankles were involved. Fluid was present in the left knee. On July 15, administration of aureomycin, 0.5 Gm. every four hours, was started but she failed to respond to this therapy, the temperature still spiking daily up to 39 C. (102.2 F.). On July 20 she was given paraaminobenzoic acid in 0.5 Gm. doses, with the total daily dose varying from 1.0 to 8.0 Gm. Use of both drugs was continued until July 31, when administration of diphenhydramine was discontinued. On August 9, daily injections of 200 mg. of pregnenolone acetate in 80 per cent sesame oil and 20 per cent benzyl benzoate were begun. By August 12, the temperature had returned to normal. On August 16 the dose of pregnenolone was reduced to 100 mg. daily. This dosage was continued until the patient was discharged from the hospital. Subjective and objective improvement of the involved joints was noted. The swelling and redness disappeared, and only slight residual stiffness remained in the wrists. On September 10 and 11 the injections of pregnenolone were missed, and on September 11 both wrists became red, tender and swollen. By September 14, after pregnenolone therapy had been resumed, the swelling of the wrists had largely disappeared, and the redness and tenderness had improved markedly.

On August 12 the mass in the left lower part of the abdomen was removed, and a specimen for biopsy was taken from the rectus muscle. Microscopic examination showed an organized hematoma. The muscle tissue showed an infiltration of lymphocytes which was specially prominent about the vascular channels. The patient's weight gradually increased until at the time of discharge she weighed 138 pounds (62.6 Kg.).

On admission, the total white blood cell count was 22,500, with 85 per cent neutrophils, 7 per cent lymphocytes, 6 per cent monocytes and 2 per cent eosinophils; the sedimentation rate was 41 mm. per hour (corrected), and the hemoglobin content was 10.5 Gm. Studies of the urine showed no significant abnormalities. The serologic reaction for syphilis was negative. Neither occult blood nor parasites were found in the stools. Blood cultures were repeatedly sterile. On June 27, total serum proteins were 5.8 Gm. per hundred cubic centimeters (albumin 3.5 Gm. and globulin 2.3 Gm., with an albumin-globulin ratio of 1.5). On June 21 a determination of prothrombin time showed 63 per cent of normal prothrombin activity. The van den Bergh test showed a serum content of direct-reacting

bilirubin of 0.4 mg. and of indirect-reacting bilirubin of 0.9 mg. per hundred cubic centimeters. The basal metabolic rate was + 3 per cent on July 29. Results of routine agglutination tests were negative. Gastric washings were repeatedly free from acid-fast bacilli; guinea pig inoculations were unsuccessful. Repeat determinations of serum proteins on August 10 gave the following values: total, 6.2 Gm. per hundred cubic centimeters (albumin 3.6 Gm. and globulin 2.6 Gm.). A van den Bergh test on September 22 showed 0.05 mg. of direct-reacting bilirubin and 0.3 mg. of indirect-reacting bilirubin per hundred cubic centimeters of serum. A determination of urinary urobilinogen on the same date showed 0.5 Ehrlich unit in a two hour specimen. Tests of hepatic function showed a negative cephalin flocculation reaction at twenty-four and forty-eight hours, a thymol turbidity of 3 units and a negative flocculation reaction.

An electrocardiogram taken on June 28 was normal, and a roentgenogram of the chest disclosed no abnormalities. Serial roentgen studies of the upper part of the gastrointestinal tract, roentgenograms made after a barium sulfate enema and an intravenous pyelogram showed nothing significant.

CASE 8.—H. M. K., a 23 year old white clerk was well until 1945, when he began having episodes of pain low in the back on turning in bed. In June 1946 he had acute pain and stiffness in the lower part of the back, with radiation to the left leg "like a red hot rod." Low back pain continued for several weeks. In 1947 he began to have morning stiffness, which cleared up during the day with activity. In the spring of 1948, symptoms became more acute. Roentgenograms of the back were made, but no treatment was prescribed. From then on, symptoms became severer; pain in the lower part of the back was persistent, and breathing became painful; laughing and coughing produced acute thoracic pain. He was unable to sleep because he could not find a comfortable position in bed. He lost weight and complained of fatigue and depression.

On admission to Letterman General Hospital in February 1949, he walked stiffly with the back held rigidly. Nutrition was poor. The lumbar curve was completely lost, and there was a rounded dorsal kyphosis. The erector spinae muscles stood out and were extremely spastic. There was tenderness over the sacroiliac joints and the lumbar spines. Flexion of the spine was completely lost. The chest expansion was 1.25 cm. The height was 175 cm. and the weight 67 Kg. Laboratory studies on February 16, revealed a hemoglobin content of 14 Gm. per hundred cubic centimeters; leukocytes 7,700 with a differential count of 69 per cent segmented neutrophils, 2 per cent banded forms; 21 per cent lymphocytes; 6 per cent mononuclears; 3 per cent eosinophils. Sedimentation rate was 19 mm. per hour (Wintrobe). His urine was normal. Roentgenograms of the cervical, thoracic and lumbar portions of the spine showed only the typical changes of spondylarthritis in the sacroiliac joints.

All urine was collected and preserved with toluene, and two three day pools were examined for neutral 17-ketosteroids. Intragluteal placebo injections were given for six days without change in symptoms or physical signs. At the end of this period, 100 mg. of pregnenolone acetate was given daily, as shown in figure 5. There was clinical improvement coincident with the return of the 17-ketosteroids to normal levels. Muscle spasm decreased 25 per cent, and mobility of the lumbar and thoracic portions of the spine increased a similar amount within five days. The patient was able to sleep all night; pain on breathing was abolished, and the patient became so desirous of doing tasks about the ward that he had to be cautioned against overactivity. Without the patient's knowledge, placebo injections of sesame oil were instituted in place of pregneno-

lone, and there was a return of pain and stiffness and the ketosteroid excretion increased again. With the reinstitution of pregnenolone medication, there was a slight temporary increase in the 17-ketosteroid excretion, then a fall to normal with abatement of symptoms.

At the end of eight weeks the patient was free of symptoms, but there was still residual muscle spasm, and so roentgenotherapy was instituted while the patient continued to receive pregnenolone. A dose of 1,200 r (air) was given over a period of nine days, and the patient suffered the usual effects of irradiation without evidence of further improvement. Pregnenolone apparently did not prevent the sharp rise in ketosteroid excretion which usually follows radiation therapy. He was discharged at the end of twelve weeks, and at that time he was entirely free of pain, had normal range of motion in the spine and had but barely perceptible muscle spasm in the lumbar region.

When he was reexamined, five weeks later, he was still free of pain and had no limitation of movement of the spine, but there was definite muscle spasm and ketosteroid excretion had increased over three day period to an average of 25

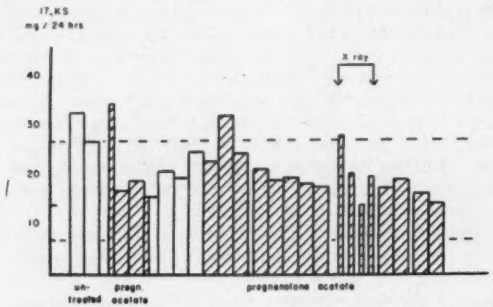

Fig. 5.—Excretion of 17-ketosteroids in case 8.

mg. in twenty-four hours. Although directed to return for a check on his condition, he was seen only once, six months after leaving the hospital. He stated that there had been no return of symptoms, but he has not returned for reexamination.

Case 9.—P. A. R., a 57 year old male American farmer, was first seen July 6, 1949. Until the past year he had pruned trees, carried sacks weighing 100 pounds (45 Kg.) and had done other work of a small fruit ranch. Ten months before examination, he began to fatigue easily, lose weight and have severe articular pain accompanied with limitation of joint mobility, and by the time of his first visit he had become so weak and had so much pain and stiffness that he could do no work.

On initial physical examination his weight was 134 pounds (61 Kg.) and his height 67½ inches (171.5 cm.). He walked with a limp because of a stiff, partially flexed right knee. All movements were slow and painful, and there was marked emaciation with striking atrophy of the shoulder muscles. Shoulder movement was limited to arm flexion of 45 degrees with the trunk; abduction was practically impossible. Movements of the spine were limited. There was tenderness over the thoracic spines, and the lumbar curve was obliterated. The skin temperature

of the right knee was increased, and fluid was present; with assistance, flexion could be performed to 45 degrees and extension to 170 degrees. Atrophy of the quadriceps extensor was extreme.

The urine was normal, and the serologic reactions were negative. A blood count showed 12.9 Gm. of hemoglobin per hundred cubic centimeters; a hematocrit reading of 45 per cent, and 10,000 white cells, with the following differential count: neutrophils 78 per cent (segmented forms 76 per cent, banded forms 1 per cent, juveniles 1 per cent), lymphocytes 13 per cent, mononuclears 4 per cent, eosinophils 4 per cent and basophils 1 per cent. The sedimentation rate was 33 mm. per hour (Wintrobe).

The patient was admitted to Stanford University Hospital on July 28, and remained there through August 13. During this entire period, his temperature was elevated in the afternoon, from 37.8 to 38.2 C. (100 to 101 F.). Crystalline pregnenolone in aqueous suspension with aluminum phosphate was given daily in doses of 200 mg. (injections at 8 a. m. and 4 p. m.). No subjective or objective improvement occurred in this period.

TABLE 4.—*Blood Counts in Case 9*

	Hemoglobin, Gm./100 Ce.	Hematocrit, %	White Cells	Differential Count					Sedimentation Rate (Wintrobe) (Mm./Hr.)
				Neutrophils					
				Segmented, %	Band %	Juvenile, %	Lymphocytes, %	Eosinophils, %	
7/ 6/49	12.9	45	10,100	76	1	1	13	3	30
8/26/49	14.8	..	12,300	83	1	0	12	2	40
9/16/49	14.1	42	8,600	60	2	0	32	4	47
9/30/49	14.1	41	11,900	77	3	0	15	3	39
11/ 4/49	13.2	..	7,900	82	5	0	35	4	35

From August 13 to 26 he was ambulant at home and received one daily injection of 100 mg. of pregnenolone acetate. On August 20, subjective improvement was noted by the patient; his back was freer, and pain in the shoulders and right knee had gone. There was still fluid in the right knee, with limitation of motion although active use was better. There was no tenderness over the spine. On August 26, the dose of pregnenolone acetate was increased to 150 mg. daily, and on September 10 the patient felt as if "something were lifted from him." He no longer felt tired; pain and stiffness disappeared; fluid disappeared from the right knee, and there was a full range of active motion with pain. The 150 mg. dosage was continued until September 30. His strength increased. Though the shoulders still showed some loss of elevation, there was no pain within the possible range, and the patient jumped up and down to demonstrate the absence of disability in the right knee. At this time, the dosage of pregnenolone acetate was reduced to 100 mg. every second day, and this schedule was continued to October 21. By that time he was again driving his own truck and lifting sacks of chicken feed, a feat impossible for months before. Objectively, the right knee was normal, and, while the lumbar portion of the spine remained fixed, there was no muscle spasm in the back. He could now move both arms without pain, elevating them to an angle of 135 degrees with the trunk and abducting them 120 degrees. Sexual desire and potency, which had been absent for many months, returned early in October.

Although this patient has recovered from symptoms and objective findings of active rheumatoid arthritis and blood counts show continued improvement, the elevated sedimentation rate suggests remaining activity.

Blood counts on this patient were quite variable.

CASE 10.—In February 1949, J. D., a 19 year old unmarried white woman, began to have a rather severe pain low in the back and the inner aspect of her right thigh, which obliged her to stay in bed for one week. The pain gradually disappeared, and she was able to return to her work as an usherette until June 1949, when pain developed in her left temporomandibular joint, left side of her neck and low in the left side of her back. She was hospitalized at San Francisco Hospital, where a diagnosis of rheumatoid arthritis was made. Her past history was noncontributory except for recurrent sore throats.

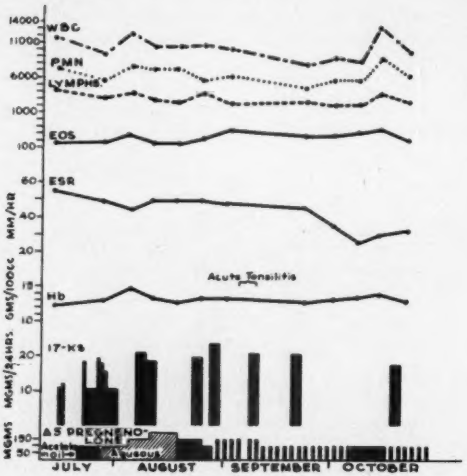

Fig. 6.—Laboratory data for case 10.

Physical examination on July 9 revealed a slight woman who appeared weak and fatigued. There was slight stiffness of the neck with pain and tenderness on the left, particularly on rotation of the neck to the right. There was marked tenderness over the left sacroiliac joint, and flexion of the back was markedly limited. There was great spasm of the erector spinae muscles in the lumbar area. Straight leg raising caused acute pain in the lumbosacral region, greater on the left. There was tenderness over the left temporomandibular joint, but the other joints were normal. Hematologic studies revealed a hemoglobin content of 12.3 Gm. per hundred milliliters and 11,300 white blood cells, neutrophils 61 per cent, lymphocytes 35 per cent, mononuclears 3 per cent and eosinophils 1 per cent. The sedimentation rate was 54 mm. per hour (Wintrobe), and the hematocrit reading was 35 per cent. Roentgenograms showed changes in the apophysial articulations of the cervical and lumbar portions of the spine and sclerosis of the left sacroiliac joint.

From July 20 to 27 she was given 100 mg. of pregnenolone acetate in sesame oil intramuscularly daily. An aqueous suspension of crystalline pregnenolone was then substituted in a dose of 100 mg. daily for one week; the dose was then increased to 150 mg., and then to 200 mg., as shown in figure 6. Pain and stiffness in the neck were relieved, and most of the pain and tenderness low in the back and muscle spasm disappeared. After five weeks of therapy with pregnenolone, when the patient was almost asymptomatic, administration was stopped, and there was a slight recurrence of pain low in the back and stiffness in the neck. This gradually disappeared when pregnenolone was again given in doses of 150 mg. in oil at daily intervals. After three weeks, the dosage was reduced to 100 mg. every other day, and this dosage has been continued to the present except for one week when daily injections were given because of aching in the right hand.

With intramuscular injections of pregnenolone, this patient's pain in the sacroiliac region and stiffness of the neck have improved to the point that she is hardly conscious of them. She feels well generally, has gained weight and is sleeping well. Her menstrual periods have been normal. There has been no change in the skin or distribution of the hair, nor has there been any pathologic change in her blood picture. Figure 6 shows blood counts, sedimentation rates, ketosteroid excretion and pregnenolone dosage.

CASE 11.—R. A., a 28 year old white sergeant, was well until January 1946, when he noticed a sudden "catch" in his left hip. This bothered him when he walked and on bending over, but it lasted only a few seconds. From January to August 1946, the pains became more frequent and increased in intensity until by August they had become almost constant and involved the lower part of his back and both hips. Since that time he has had such pain almost constantly. In August and September 1946 the patient was hospitalized at Scott Field, Ill., where he was treated with physical therapy, with only slight relief. A diagnosis of rheumatoid spondylitis was made, and he was transferred to Percy Jones General Hospital. He was then given a course of roentgen therapy to his back, receiving twelve treatments of unknown amount. After the roentgen therapy he continued to have symptoms as before. He was hospitalized again at the Army and Navy General Hospital, Hot Springs National Park, Ark., from February to April 1948, receiving physical therapy during that period, again with little relief.

Significant physical findings on entrance to Letterman General Hospital were mild scoliosis of the spine with the convex curve to the left in the thoracic and upper lumbar region, the right iliac crest 2 cm. higher than the left and tenderness and slight spasm in the erector spinae muscles in the lower thoracic and upper lumbar region. There was tenderness to percussion over the vertebrae in this region. On forward bending, the back was held flat from the eighth thoracic vertebra to the sacral area. Most of the bending was done at the hips. Neurologic examination disclosed nothing significant.

Course in the Hospital: At the time of admission, the patient complained of severe pain low in the back and pain in the chest on deep inspiration. Acetylsalicylic acid 0.6 Gm. was given every four hours with moderate relief of pain. On August 2, a regimen of active back flexion exercises following heat over the lower part of the back for twenty minutes daily was instituted. He also performal postural exercises in the ward. No improvement of the back was noted on this therapy. On August 23, daily intramuscular injections of 100 mg. of pregnenolone acetate in sesame oil were begun, and they were continued through September 27. No subjective or objective improvement was noted during this period. On September

27 the dosage of pregnenolone was increased to 200 mg. daily, given in two injections. This therapy was continued to October 30, and during this period no subjective or objective change was noted.

Laboratory studies on admission showed a total white blood cell count of 10,500, with 83 per cent neutrophils, 11 per cent lymphocytes, 2 per cent monocytes and 4 per cent eosinophils. The hemoglobin content was 11.7 Gm., and the corrected sedimentation rate was 38 mm. per hour. A Kahn test for syphilis elicited a negative reaction; the urine was normal; the total serum proteins were 7.4 Gm. per hundred cubic centimeters (albumin 4.9 Gm. and globulin 2.5 Gm.). A roentgenogram of the chest showed no abnormalities, and roentgenograms of the lumbosacral region, pelvis, and thoracic and lumbar portions of the spine showed minimal changes of rheumatoid spondylitis.

CASE 12.—M. S., a 29 year old married woman, entered Stanford University Hospital on Oct. 10, 1949, with a history of having been well until two years before, when her left knee became swollen and painful and purulent material was aspirated from it. No Neisseria organisms were isolated from this fluid. The swelling and pain in her knee continued in spite of penicillin treatment, and in May 1948 a synovectomy was performed at the San Francisco Hospital. About one year before entry aching had developed in her knees, ankles, hands and wrists and fingers, which had become intermittently swollen and painful. Six weeks before entry, she contracted what she thought was a cold, and her legs and face became swollen. She was admitted to San Francisco Hospital on Sept. 7, 1949 and remained there until September 26. She was found to have bilateral pleural effusion and hypertension.

The urine contained albumin (3 to 4 plus), many granular casts, 2 to 4 white blood cells and 100 plus red blood cells. Blood studies revealed 11.0 Gm. of hemoglobin, 4,000,000 red cells and 6,200 white cells, with neutrophils (segmented forms) 64 per cent, eosinophils 4 per cent, lymphocytes 26 per cent and monocytes 6 per cent. The hematocrit reading was 34 per cent, and the sedimentation rate was 34 mm. per hour (Wintrobe). The blood urea level was 30 mg. per hundred cubic centimeters and the cholesterol level 110 mg. The albumin-globulin ratio was 3.56:2.119. The antistreptolysin titer was 50 units per cubic centimeter.

A roentgenogram of the chest on September 8 revealed marked pulmonary edema with bilateral pleural effusion, both of which had cleared by September 21 after aspiration of fluids from the chest and use of a low salt, low protein diet. An electrocardiogram revealed abnormal T waves suggesting myocardial damage.

On discharge, the patient continued to have pain and swelling of her joints, and she was admitted to the hospital for study and treatment. Her past history revealed that she had mild "growing pains" as a child, that she had four living children and that she had been pregnant ten times.

On entry, she was pale, walked with great care and limped considerably. Her heart was enlarged 2 cm. beyond the midclavicular line. The remainder of the general physical examination disclosed normal conditions except for her extremities. Both wrists were swollen and hot and extremely tender to palpation and showed great limitation of motion. In the right wrist dorsiflexion was limited to 30 degrees and flexion to 25 degrees, and in the left dorsiflexion was limited to 15 degrees and flexion to 20 degrees. There was some atrophy of the interosseus muscles. The right elbow was painful but not swollen. The right knee was distended with fluid and warm; it extended and flexed well. Both feet and ankles were swollen and tender, and the metatarsal areas were tender. Both feet were wet and clammy. Results of laboratory work are shown in table 5.

Administration of pregnenolone in sesame oil, 100 mg. intramuscularly twice daily, was begun on October 15, and this was continued until October 26, when it was reduced 100 mg. daily for two days. On October 21, the patient had gained considerably in strength and was having less pain, but the swelling of the joints remained. She felt much better in general, and her spirits were much improved. On October 29, she was given placebo injections and these were continued until November 3; during that period she had recurrence of some pain and weakness. She was again given 150 mg. of pregnenolone daily until November 9, at which time the dose was doubled, without effect. She was discharged on November 15. During her entire stay she had daily temperatures up to 38 C. (100.1 F.). Her knee was aspirated four times.

However, since her discharge from the hospital she has improved greatly; the swelling of her joints has diminished considerably and her pain almost completely disappeared. She now feels well.

An Addis count of the urine gave the following values per 10 cc. of urinary sediment: protein, 0.1 Gm.; red blood cells, 129,000,000; white blood cells, 9,000,000, and red cell casts, 100,000.

TABLE 5.—*Blood Counts in Case 12*

						Differential Count					
						Neutrophils					
	Sedimentation Rate	Hematocrit, %	Red Cells	Hemoglobin, Gm./100 Cc.	White Cells	Segmented, %	Stab, %	Eosinophils, %	Basophils, %	Lymphocytes, %	Mononuclears, %
10/10/49	46	35	4,400,000	12.4	12,100	44	15	1	4	29	7
10/13/49	..	..	4,300,000	13.0	.....	..	..	..	..	..	..
10/18/49	..	..	4,800,000	13.7	14,000	49	10	..	3	30	8
10/19/49	61	..	.....	....	.....	..	..	..	..	..	..
10/21/49	..	..	5,100,000	10.9	12,000	59	5	7	..	18	11
10/24/49	56	32	4,200,000	10.4	11,800	54	6	4	..	29	5
10/26/49	..	..	3,900,000	10.5	10,300	47	5	4	..	41	3
10/27/49	..	34	4,900,000	12.2	.....	..	..	..	..	..	..
10/28/49	..	..	3,400,000	10.5	11,500	44	8	5	..	35	7
10/29/49	56	34	.....	....	.....	..	..	..	..	..	..
10/31/49	..	..	4,200,000	11.0	12,900	59	7	6	1	42	4
11/ 2/49	..	..	4,000,000	11.0	12,900	47	7	4	1	36	4
11/14/49	40	38	3,800,000	11.2	9,900	68	4	3	..	23	2

The blood urea nitrogen level was 33 mg. per hundred cubic centimeters; creatinine level, 1.19 mg.; calcium level, 10.7 mg.; phosphorus level, 2.4 mg., and cholesterol level, 287 mg. Total proteins measured 7.1 Gm. with an albumin-globulin ratio of 3.6:3.5. The antistreptolysin titer on November 3 was 166 units per cubic centimeter. Routine agglutination tests on October 31 gave negative results. Hinton and Wassermann tests of the blood on October 13 elicited negative reactions. Sheep cell agglutination tests gave positive results in a dilution of 1:56.

On October 13 study of joint fluid showed a white blood cell count of 55,000, of which 92 per cent were neutrophils and 8 per cent lymphocytes; on November 5 the count was 7,350, with the same differential distribution of cells.

Blood counts are shown in table 5.

CASE 13.—I. D. S., a 20 year old white male private, was well until March 1948, at which time he first noticed pain and stiffness in both "hip regions," aggravated by exercise. This was followed by gradual increase in pain and stiffness in both hips and the lower part of the spine. By April 1949, he was having much morning stiffness in the back and hips, and intermittent pains in the same areas. He was

frequently awakened at night with painful muscle spasms in his back. He was treated with heat to his back, and active exercise in the gymnasium. The symptoms continued to become progressively worse. On June 16 he had a severe attack of pain and muscle spasm in his back which was unsuccessfully treated with injections of procaine hydrochloride, and on June 24 he was admitted to Letterman General Hospital. The patient had lost 15 pounds (6.8 Kg.) in the eight months prior to admission.

The weight was 129 pounds (58.5 Kg.). There was marked spasm of the erector spinae muscles in the lower thoracic and lumbar area bilaterally, visible at a distance, together with boardlike rigidity. The lumbar curve was flattened, and there was moderate anterior bowing of the cervical portion of the spine. Motion of the spine in any direction was markedly limited and painful. Forward flexion was limited to 30 degrees and was done entirely at the hips. The spine did not round out from the eighth thoracic vertebra to the sacrum. Chest expansion was limited to 2 cm.

Urinalyses disclosed no abnormalities. The Kahn test for syphilis elicited a negative reaction; an oral glucose tolerance curve on July 13 was normal; the fasting blood sugar level on November 2 was 85 mg. per hundred cubic centimeters. The spinal fluid was entirely normal. A roentgenogram of the chest showed no abnormalities, and roentgenograms of the thoracic and lumbar portions of the spine showed minimal scoliosis of the upper thoracic region, with the convex curve to the left, but otherwise they showed no pathologic change.

During his stay in the hospital the patient complained of marked stiffness and painful muscle spasm in his back which was only partially relieved by salicylates. On July 13 daily intramuscular injections of 2 cc. of sesame oil were begun as a control for future pregnenolone therapy. These were continued through July 21, and during this period no change in the patient's status was noted.

On July 22, daily intramuscular injections of pregnenolone acetate in sesame oil, 100 mg., were begun, and this therapy was continued through July 26, when the daily dose was increased to 200 mg. During this period, no subjective or objective changes were noted. On August 2 daily injections of 200 mg. of pure pregnenolone in aqueous suspension were started. These were given through August 24, when use of pregnenolone acetate in sesame oil, 200 mg. a day, was resumed. This was continued through September 6. Again, through this period no objective or subjective changes were noted in the patient's condition. On September 8 roentgen therapy to the spine was started, and three fields, which included the entire spine, were irradiated. A total of 1,500 r was given over a six day period. After this treatment the patient noted no improvement, and no objective improvement in mobility of the spine or muscle spasm was observed. At the present time, the physical condition is approximately the same as when he was admitted.

IS THERE A RELATION BETWEEN DIET AND BLOOD CHOLESTEROL?

CHARLES F. WILKINSON Jr., M.D.*
NEW YORK
ELMIRA BLECHA, M.S.
AND
ANN REIMER, M.S.
ANN ARBOR, MICH.

THE LEVEL of the blood cholesterol varies with certain disease states, and recently some workers have thought that a high level may be related to the development of atheromatosis. It has been suggested by Dock [1] and by others [2] that the amount of cholesterol in the diet is a factor in determining the concentration of this material in the blood and in the production of atheromas. Doubt has been expressed, however, concerning the importance of the dietary cholesterol as a controlling factor of the blood level, and also as to its etiologic significance in atherosclerosis.[3]

Many assumptions of those favoring a dietary factor in the production of atherosclerosis have been based on the fact that in certain races whose members ingest less cholesterol and animal fat this change in the arteries is less prominent. Since so many other known and unknown variables may be present, it is obvious that any conclusion regarding this relation may be incorrect.

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* Formerly from the Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, and the W. K. Kellogg Foundation, Battle Creek, Mich.

1. Dock, W.: The Predilection of Atherosclerosis for the Coronary Arteries, J. A. M. A. **131**:875 (July 13) 1946; Coronary Disease, ibid. **134**:1197 (Aug. 2) 1947; Atherosclerosis, Bull. U. S. Army M. Dept. **8**:316 (April) 1948.

2. Leary, T.: Arteriosclerosis, Bull. New York Acad. Med. **17**:887 (Dec.) 1941. Plotz, M.: Possible Hazards of High Fat Diets in Coronary Disease, J. A. M. A. **139**:623 (March 5) 1949. Boas, E. P.; Parets, A. D., and Adlersberg, D.: Hereditary Disturbance of Cholesterol Metabolism: A Factor in the Genesis of Atherosclerosis, Am. Heart J. **35**:611 (April) 1948. Okey, R., and Stewart, D.: Diet and Blood Cholesterol in Normal Women, J. Biol. Chem. **99**:717 (Feb.) 1933.

3. (*a*) Sperry, W. M., and Schick, B.: Essential Xanthomatosis: Treatment with Cholesterol-Free Diet in Two Cases, Am. J. Dis. Child **51**:1373 (June) 1936. (*b*) Wilens, S. L.: Relation of Chronic Alcoholism to Atherosclerosis, J. A. M. A. **135**:1136 (Dec. 27) 1947. (*c*) Falk, O. P. J.: Treatment of Coronary Artery Disease: Dicumarol Therapy, ibid. **134**:491 (June 7) 1947. (*d*) Shaffer, C. F.: The Nutritional Role of Cholesterol in Coronary Arteriosclerosis, Ann. Int. Med. **20**:948 (June) 1944.

Dietary habits depend on many factors, such as the following: (*a*) economic considerations; (*b*) availability of foods; (*c*) personal likes and dislikes; (*d*) age in respect to freedom of choice; (*e*) dental repair, and (*f*) probably as important as any, the dietary habits of the family. In the present study, as many of these factors as possible were kept constant. Eighty per cent of the subjects lived in rural areas. All had economic freedom of choice. Meals were planned, cooked and served only by the housewife in each of the several groups. The study was of sufficient duration to eliminate seasonal variation. The groups observed were cautioned not to change their eating habits and to record everything they ate. Comparisons of individual subjects thus studied are undoubtedly superior to broad generalizations formulated without an effort to recognize or control known variables.

During the investigation of a kindred (family group) in which essential familial hypercholesteremia was present,[4] an opportunity was afforded one of us (C.F.W.) to determine the effect of dietary composition on blood cholesterol level. Because this family was large and cooperative, and because four generations were available, it was an ideal group for this study. Of 91 persons who kept records of dietary intake, 83 were observed with sufficient completeness to be included in this report.

Essential familial hypercholesteremia [4] is a metabolic disorder characterized by the increased total blood cholesterol and by a normal percentage of cholesterol esters. The other blood lipids are little affected with the exception of the phospholipids, which are also increased. This condition is transmitted as an "incomplete" dominant character, and the homozygous abnormal person not only has xanthoma tuberosum but is subject to early atheromatosis. The heterozygous abnormal person has hypercholesteremia and may or may not have xanthelasma, but he does not have xanthoma tuberosum. The present concept of the gene pairing, the method of transmission and possible matings is shown in figure 1.

Figure 2 represents the age distribution of the 159 persons studied in detail in the large family group of 282. The study presented here includes 83, or 52.2 per cent, of that group. They were selected at random, and usually before the values for blood cholesterol were known. We felt justified, therefore, in using certain data collected during the larger study.

Families were chosen for observation in which there were people with essential familial hypercholesteremia as well as normal subjects. Usually the mother kept the records for the entire family, measuring and recording the types and quantities of food used by the individual

4. Wilkinson, C. F., Jr.; Hand, E. A., and Fliegelman, M. T.: Essential Familial Hypercholesterolemia, Ann. Int. Med. **29**:671 (Oct.) 1948.

subjects at each meal. In every case a competent dietitian taught the recorder the technic of keeping food diaries. Such information was recorded for one or more weeks during the seven months of this study. The diet diaries were then analyzed, and the component parts of the diets were calculated from accepted food tables.[5] It can be seen in figure

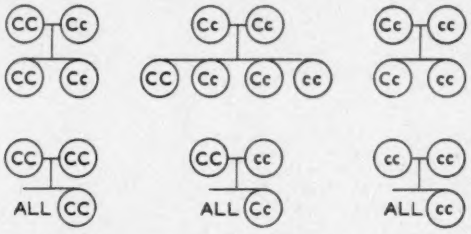


Fig. 1.—Gene pairing and method of transmission. The circles represent individual persons, and each *C* or *c* represents one of a pair of genes. Possible matings are shown as well as the predictated distribution of the offspring of each such mating. *C* indicates hypercholesteremia; *c*, normal cholesterol level; *CC*, homozygous abnormality; *Cc*, heterozygous abnormality, and *cc*, homozygous normality.

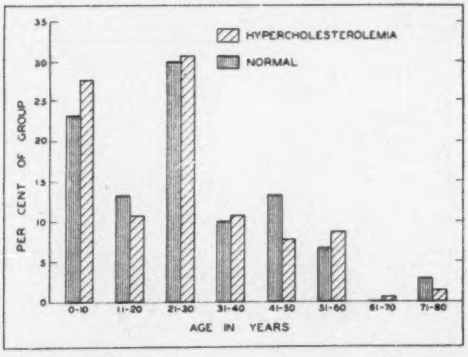


Fig. 2.—Age incidence. Only 2 of the persons with hypercholesteremia were homozygous abnormal; each was less than 20 years of age.

3 that the level of the total blood cholesterol was unrelated to the absolute amounts of carbohydrate, fat, protein and cholesterol in the diet.

5. Turner, D.: Handbook of Diet Therapy, Chicago, University of Chicago Press, 1946. Cooper, L.; Barber, E., and Mitchell, H.: Nutrition in Health and Disease, Philadelphia, J. B. Lippincott Company, 1947.

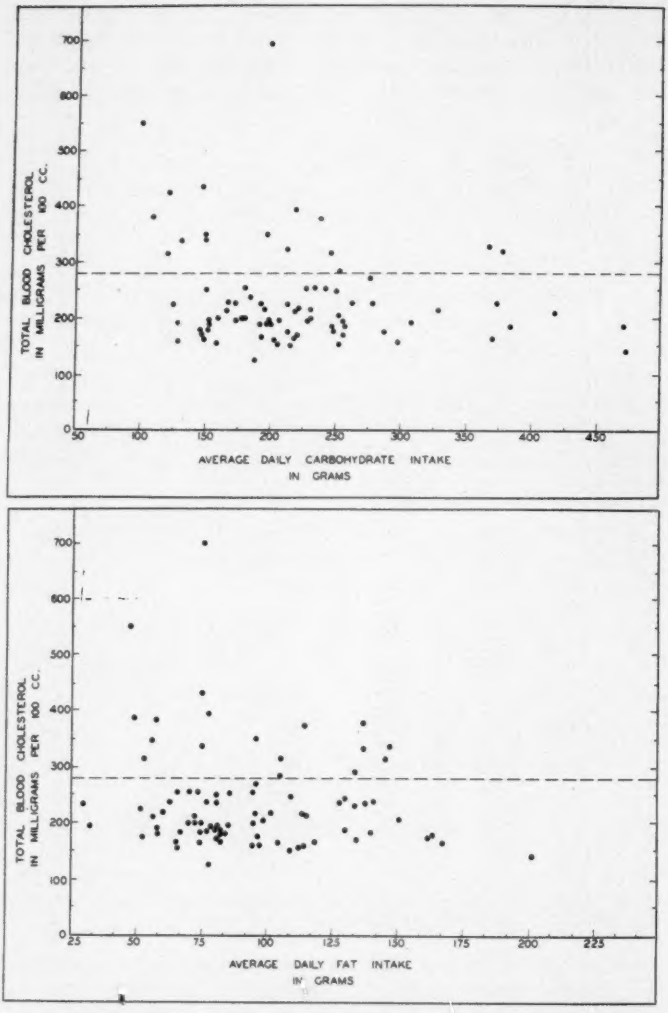
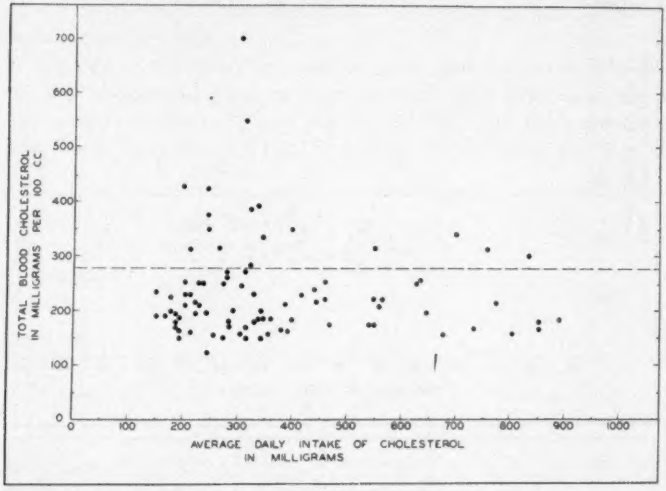


Fig. 3.—Intake of each component of the diet. The broken line designates hypercholesteremia. Total serum cholesterol levels are plotted as values from Bloor's test.

Since the ages of the subjects studied varied from less than 1 year to 59 years it was natural that the total calories consumed per day would also vary. It was concluded that a more significant comparison could be



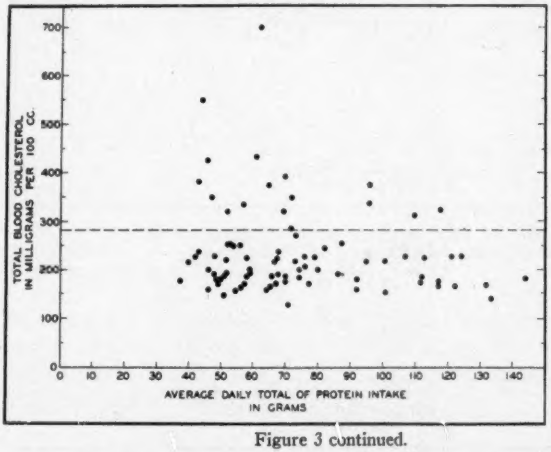


Figure 3 continued.

made when the percentage of the caloric intake resulting from each component in the diet, rather than the absolute amount of that component, was used as the variable. Figures 4 and 5 show that there was no relation between composition of the diet and total blood cholesterol level.

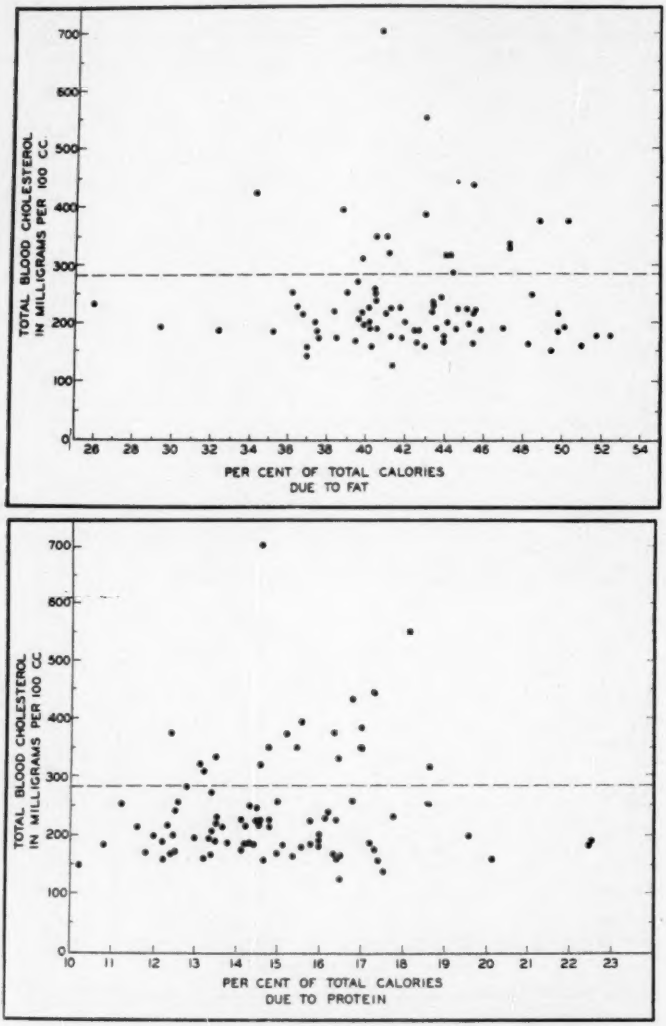


Fig. 4.—Percentage of caloric intake resulting from each component of the diet. The broken line designates hypercholesteremia. Total serum cholesterol levels are plotted as values from Bloor's test.

Hypercholesteremia per se appears to have no effect on life expectancy when it is found in heterozygous abnormality of essential familial hypercholesteremia. In the homozygous abnormal subject, however, this is not the case. Atheromatosis may develop at an early age and is not uncommonly fatal.

Results of the study of cardiovascular complications of essential familial hypercholesteremia, as found in this kinship and others, are to be presented in detail at a later date. Only 2 patients with angina pectoris were observed among the 159 studied. One of these was 59 years

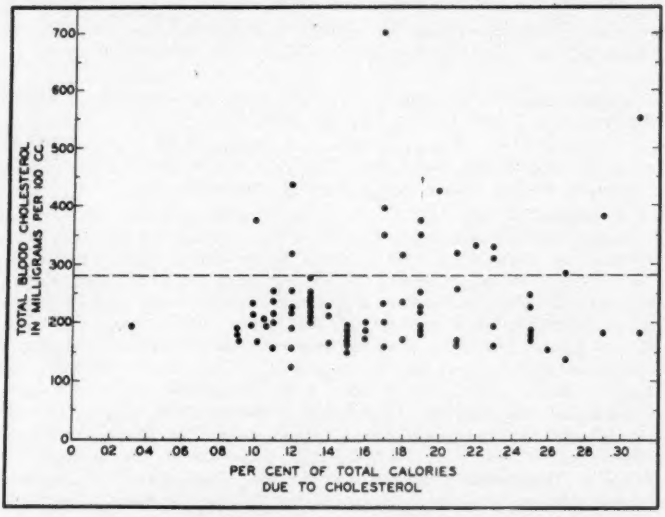


Fig. 5.—Percentage of caloric intake resulting from cholesterol in the diet. The broken line designates hypercholesteremia. Total serum cholesterol levels are plotted as values from Bloor's test.

old and had a normal blood cholesterol level. The other was a homozygous abnormal subject who was 11 years of age when seen but who had had symptoms for two years. She also had electrocardiographic signs indicative of myocardial damage.

COMMENT

Whereas our studies do not prove the complete absence of relation between the dietary intake of lipids and blood cholesterol level, they do provide additional support for that possibility.

In a recent report, Moreton [6] presented data in support of a theory that the size of the colloidal lipids in the blood is of great importance. Data published by Wilens [7] stressed the effect of a gain or loss of body weight on atheromatosis, and Bruger and his co-workers [8] called attention to the varied metabolic factors concerned. In a recent report, Faber [9] showed that hypertensive cardiovascular disease is a factor in the formation of aortic atheromas as much as, if not more than, hypercholesteremia.

When one considers the relatively large amount of cholesterol known to be synthesized,[10] and when data such as Shaffer [3d] and Holman [11] presented is evaluated, our data add to the already enormous amount of evidence which shows that the problem is a complex one for which no simple answer should be expected.

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6. Moreton, J. R.: Physical State of Lipids and Foreign Substances Producing Atherosclerosis, Science **107**:371 (April 9) 1948.

7. Wilens, S. L.: Bearing of General Nutritional State on Atherosclerosis, Arch. Int. Med. **79**:129 (Feb.) 1947; The Resorption of Arterial Atheromatous Deposits in Wasting Disease, Am. J. Path. **23**:793 (Sept.) 1947.

8. Bruger, M., and Fitz, F.: Experimental Atherosclerosis: I. Effect of Prolonged Administration of the Thyrotropic Factor of the Anterior Lobe of the Pituitary on Experimental Atherosclerosis in the Rabbit, Arch. Path. **25**:637 (May) 1938. Flexner, J.; Bruger, M., and Wright, I. S.: Experimental Atherosclerosis: II. Effect of Thiamine Hydrochloride and Ascorbic Acid on Experimental Atherosclerosis in Rabbits, ibid. **31**:82 (Jan.) 1941. Nyboer, J.; Bruger, M., and Rabson, S. M.: Experimental Atherosclerosis: III. Electrocardiographic Studies and Pathologic Changes in the Hearts of Cholesterol-Fed Rabbits, Am. Heart J. **21**:657 (May) 1941. Ludden, J. B.; Bruger, M., and Wright, I. S.: Experimental Atherosclerosis: IV. Effect of Testosterone Propionate and Estradiol Dipropionate on Experimental Atherosclerosis, Arch. Path. **33**:58 (Jan.) 1942. Bruger, M.; Wright, I. S., and Wiland, J.: Experimental Atherosclerosis: V. Effect of Testosterone Propionate and Estradiol Dipropionate on Cholesterol Content of Blood and Aorta in Castrate Female Rabbits, ibid. **36**:612 (Dec.) 1943. Member, S.; Bruger, M., and Oppenheim, E.: Experimental Atherosclerosis: VI. Effects of Various Bile Acids on Cholesterol Levels, ibid. **38**:210 (Oct.) 1944. Bruger, M.: Experimental Atherosclerosis: VII. Effect of Vitamin E, Proc. Soc. Exper. Biol. & Med. **59**:56 (May) 1945. Member, S., and Bruger, M.: Experimental Atherosclerosis: VIII. The Effect of Feeding Olive Oil on the Absorption and Deposition of Cholesterol, Arch. Path. **40**:373 (Dec.) 1945. Rosenkrantz, J. A., and Bruger, M.: Experimental Atherosclerosis: IX. Effect of Prolonged Feeding of Egg Yolk Powder in Rats, ibid. **42**:81 (July) 1946.

9. Faber, M.: The Cholesterol Content of the Human Aorta in Relation to the Serum Cholesterol Concentration, Acta med. Scandinav. **125**:418, 1946.

10. Bloch, K., and Rittenberg, D.: On the Utilization of Acetic Acid for Cholesterol Formation, J. Biol. Chem. **145**:625 (Oct.) 1942; An Estimation of Acetic Acid Formation in the Rat, ibid. **159**:45 (June) 1945.

11. Holman, R. L.: Prevention of Experimental Arterial Lesions by Cholesterol, Federation Proc. **5**: (no. 1, pt. 2) 223, 1946.

SUMMARY AND CONCLUSIONS

Eighty-three persons, from a kindred in which essential familial hypercholesteremia was present and using a diet of choice, were studied.

1. The absolute amount of carbohydrate, fat, protein and cholesterol in the diet had no demonstrable relation to the level of total serum cholesterol.

2. It was not possible to demonstrate that the percentage of total calories supplied by the various dietary constituents was related to the level of total serum cholesterol.

When hypercholesteremia is due to the heterozygous abnormality of essential familial hypercholesteremia, no adverse prognosis can be postulated. This is not true with the homozygous abnormality.

Hypercholesteremia per se has no demonstrable effect on life expectancy.

The significance of these findings in relation to atheromatosis is discussed.

477 First Avenue (16).

CONCENTRATIONS OF CHOLESTEROL, TOTAL FAT AND PHOSPHOLIPID IN SERUM OF NORMAL MAN

Report of a Study with Special Reference to Sex, Age and Constitutional Type

VALDEMAR KORNERUP, M.D.
SØNDERBORG, DENMARK

THE OBJECT of the investigation reported in the present paper was to procure normal material for the determination of total cholesterol, free cholesterol, total fat and phospholipid in human serum. In no previous investigation were all the following demands fulfilled: (1) application of modern analytic methods, insuring complete extraction of the serum lipids; (2) exclusion of individual subjects presenting xanthelasma and familial hypercholesteremia and persons in whose families such conditions were found, and (3) payment of proper attention not only to sex and age but also to constitutional type.

Serum lipids occur mainly in the following forms: (1) cholesterol and its esters, (2) "total fatty acids" (chiefly fatty acids, and smaller amounts of neutral fat) and (3) phosphatides (almost exclusively lecithin, small amounts of cephalin and minimal amounts of sphingomyelin).

The literature contains numerous reports on investigations on serum cholesterol, whereas only a few publications have been concerned with the remaining lipid fractions.

The values obtained from recent and comprehensive groups of normal material were fairly concordant, being on an average well over 200 mg. of total serum cholesterol per hundred cubic centimeters of blood, with a considerable range of variation (from 109 to 428 mg.), and about 27 per cent of free cholesterol in the total cholesterol.[1] The average fasting value for total lipids was stated to be about 700 mg. per hundred cubic centimeters, ranging from 263 to 1,413 mg. (Page and others[1b] found 2,341 mg. per hundred cubic centimeters in a single patient by the gasometric method), and that for phospholipid was about 7 mg. or 1.8 to 16.6 mg.[1b,d]

From the Medical University Clinic, Aarhus.

1. (*a*) Mühlbock, O., and Kaufmann, C.: J. Exper. Med. **102**:461, 1938. (*b*) Page, I. H.; Kirk, E.; Lewis, W. H.; Thomsen, W. R., and van Slyke, D. D.: J. Biol. Chem. **111**:613, 1935. (*c*) Sperry, W. M.: ibid. **114**:125, 1936. (*d*) Kornerup, V.: Nord. med. **16**:3300, 1942.

It has proved difficult to come to an agreement regarding the upper normal limit for serum cholesterol. Even the results obtained by modern investigators differ a great deal, depending mainly on the extraction technic. Man and Gildea's modification of Bloor's ether-alcohol extraction method [2] and Schönheimer and Sperry's alcohol-acetone extraction method [3] give complete extraction, whereas extraction with chloroform (Teilum [4]) gives lower values. On the other hand, Page and others [1b] and Sperry [1c] found values up to nearly 400 mg. in their normal material, but these values are no doubt too high to be regarded as normal. Such high values may be due to the occurrence of xanthelasma or essential hypercholesteremia in their series. This is indeed probable, as it is possible to find persons with essential hypercholesteremia but with no xanthomatous manifestation and it was also demonstrated by me [1d] that persons without xanthelasma palpebrarum in whose families that anomaly occurs seem to have slightly elevated serum cholesterol levels. The problems in relation to these matters will be taken into consideration later.

Each person has fairly constant serum cholesterol values under normal conditions, independent of the ordinary intake of food.[5]

Unlike cholesterol, fatty acid and phospholipid (and consequently total lipids) will rise to a maximum within four or five hours after a meal rich in fat.[6]

Serum lipids are not subject to seasonal variations.[7] Some writers claimed to have observed a fall in the values at the time of menstruation.[8] Such a fall, however, was not found by Man and Gildea.[7b] Pregnancy involves a rise in serum cholesterol levels.[9]

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2. Man, E. B., and Gildea, E. F.: J. Biol. Chem. **99**:43, 1932.

3. Schönheimer, R., and Sperry, W. M.: J. Biol. Chem. **106**:745, 1934.

4. Teilum, G.: Om hormonal cholesterinæmi, med særligt henblik paa sexualhormonernes virkning paa blodets totalcholesterindhold, Copenhagen, Ejnar Munksgaards Forlag, 1940.

5. (*a*) Gardner, J. A., and Gainsborough, H.: Biochem. J. **21**:130, 1927. (*b*) Bruger, M., and Somach, I.: J. Biol. Chem. **97**:23, 1932. (*c*) Turner, K. B., and Steiner, A.: J. Clin. Investigation **18**:45, 1939.

6. (*a*) Brun, G.: Acta psychiat. et. neurol., 1940, supp. 22, p. 3. (*b*) Nissen, N. J.: Studies on Alimentary Lipæmia in Man, Copenhagen, Levin & Munksgaard, 1933.

7. (*a*) Turner and Steiner.[5c] (*b*) Man, E. B., and Gildea, E. F.: J. Biol. Chem. **119**:769, 1937. (*c*) Sperry, W. M.: ibid. **117**:391, 1937.

8. Mühlbock and Kaufmann.[1] Okey, R., and Boyden, R. E.: J. Biol. Chem. **72**:261, 1927.

9. (*a*) Mühlbock and Kaufmann.[1] (*b*) Grigaut, A.: Le cych de la cholesterinæmie, Thesis, Paris, 1913. (*c*) Teilum, G.: Hospitalstid. **77**:140, 1934. (*d*) Proost, J. B.: Acta med. Scandinav. **116**:396, 1944.

SEX AND AGE

The values are generally stated to be slightly higher in female than in male subjects. The difference, however, is small.[10]

It is generally agreed that children present lower cholesterol values, as a rule under 200 mg. per hundred cubic centimeters (by older methods).[11] Sperry [12] found total cholesterol values ranging from 71 to 190 mg. (the average range was 133 ± 25 mg.) in 63 newborn babies from one to twenty-five days old by a modern analytic method.

According to Page and others,[1b] no changes are found in the serum lipids of adult males. Other investigators obtained different results. Melka,[13] for instance, found higher serum cholesterol values in men over the age of 55. Tschernorutzky [14] observed a rise in serum cholesterol after the age of 40. Mühlbock and Kaufmann [1] found increased serum cholesterol values in women after the menopause. Proost [9d] likewise found higher phosphatide and cholesterol values in elderly persons.

TYPE OF CONSTITUTION

As early as 1927, Mjassnikow [15] found that the average serum cholesterol concentration in 10 normal "hypersthenics" (4 males and 6 females) was 50 mg. higher than in 10 normal "asthenics" (2 males and 8 females). In hypersthenic patients with one or several of the diseases affecting chiefly this type (uratic arthritis, obesity, hypertensive cardiovascular disease, asthma, arteriosclerosis or gallstones) the serum cholesterol value was above the normal for this constitutional type.

The results of these investigations were borne out by Tschernorutzky [14] and two of his collaborators, Glinka-Tschernorutzkaja and Jackson.

Gildea, Kahn and Man,[16] by more modern analytic methods, found the concentration of fatty acid in the serum higher in pyknic types than in leptosomes. The cholesterol concentration in the serum of males likewise seemed to be higher among pyknic types than among leptosomes

10. Teilum.[4] Gardner, J. A., and Gainsborough, H.: Biochem. J. **22**:1048, 1928.

11. Offenkrantz, F. B., and Karshan, M.: Serum Cholesterol Values for Children, Am. J. Dis. Child. **52**:784 (Oct.) 1936. Ward, K. M.: Arch. Dis. Childhood **6**:329, 1931.

12. Sperry, W. M.: Cholesterol of Blood Plasma in Neonatal Period, Am. J. Dis. Child. **51**:84 (Jan.) 1936.

13. Melka, J.: Zentralbl. f. inn. Med. **48**:704, 1927.

14. Tschernorutzky, M. W.: Ztschr. f. Konstitutionslehre **15**:134, 1931.

15. Majassnikow, A. L.: Ztschr. f. klin. Med. **105**:228, 1927.

16. Gildea, E. F.; Kahn, E., and Man, E. R.: Am. J. Psychiat. **92**:1247, 1936.

(230 mg. against 168 mg.). The number of cholesterol determinations was, however, too small (18 and 12 respectively) to be statistically significant. Cholesterol determinations in 19 pyknic and 16 leptosomatic women revealed no significant difference (205 mg. against 196 mg.).

Finally, some investigations by Egsgaard [17] into phospholipid in the serum of psychotic, physically normal persons may be mentioned. He found an average concentration of 6.9 of phospholipid for 17 leptosomes (6 males and 11 females) and one of 8.2 mg. for 18 pyknic types (5 males and 13 females).

The morbid conditions in which one finds hypercholesteremia and lipemia are particularly certain endocrine diseases (diabetes mellitus, mxyedema), obstructive jaundice, certain renal diseases, primarily genuine nephrosis and nephritis *mit nephrotischem Einschlag,* and, finally, essential familial hypercholesteremia and certain forms of xanthomatosis.

Subnormal lipid values in serum are found in febrile conditions and hyperthyroidism.

MATERIAL AND TECHNIC

My own series comprised 221 subjects, including 125 adults from 19 to 96 (87 men and 38 women) and 96 children from 1 to 16 years (51 boys and 45 girls). All sex-age groups were fairly equally represented except that of women from ages 40 to 60, which was not represented at all. The adults were healthy medical students, physicians, nurses and other members of hospital staffs, as well as 10 normal patients with sciatica, 11 normal patients with fractures occurring just before discharge and 32 healthy inmates of the Old Age Home in Aarhus.

The children were mainly patients admitted to the pediatric department of Aarhus Kommunehospitalet for enuresis or problems of environment.

All the subjects included in the normal series were in good health, with no family history of heart disease and, as far as it was possible to ascertain, with no xanthelasma in the family. I aimed at making sure of this fact by closely questioning the persons examined or, in the cases of the children, their parents.

All samples of serum were taken from fasting subjects. Adult women had blood samples taken during the intermenstrual phase.

The cholesterol levels were determined by Sperry's method,[16] using G. C. Brun's modification,[18] which consists of the extraction of serum with boiling alcohol and acetone and precipitation of the cholesterol with digitonin before and after saponification. Then both free and total cholesterol were determined colorimetrically by the Liebermann-Burchard test on the cholesterol digitonide.

Total fat and phospholipid were determined by the technic of G. Brun.[19] Total fat was determined by weighing, and phospholipid, photometrically, by

17. Egsgaard, J.: Nord. med. **17**:455, 1943.

18. Brun, G. C.: Acta med. Scandinav., 1939, supp. 99, p. 3.

19. Brun, G.: Bibliot. f. læger **131**:197 and 203, 1939.

the method of Lundsteen and Vermehren [20] for determination of inorganic phosphorus with amidol and ammonium molybdate after ashing of the total fat with nitrosulfuric acid in a Kjeldahl oven.

Double analyses were made in all cases, and the results of each two determinations agreed well. The standard deviations for cholesterol, total fat and phospholipid were 2, 4 and 3 per cent respectively.

The amounts of phosphatides were calculated from the phospholipid value by multiplication by 25. "Total fatty acid" (i. e., fatty acid and neutral fat) was calculated by subtracting the amounts of phosphatides and total cholesterol from that of total lipids.

Cholesterol values were determined in the serum of 117 adults (80 men and 37 women) and 95 children (51 boys and 44 girls). Values for total lipids and phospholipid were determined in the serum of 104 adults (73 men and 31 women) and 94 children (51 boys and 43 girls).

The following formulas were used for calculating the standard deviation (σ), the mean error of the series (ϵ) and the mean error of a difference (ϵ_d) between two groups (o signifies the individual observations, m the average of these, n the number of observations and Σ a sign of summation):

$$\sigma = \pm\sqrt{\frac{\Sigma o^2 - m\Sigma o}{n-1}}$$

$$\epsilon = \pm\frac{\sigma}{\sqrt{n}}$$

$$\epsilon_d = \pm\sqrt{\epsilon_1^2 + \epsilon_2^2}$$

RESULTS AND COMMENT

The results are given in tables 1, 2 and 3 and in figure 1.

The sex and age differences with regard to serum lipid values were small and generally insignificant (table 4).

Sex.—Like other investigators, I found a tendency toward higher values for serum lipids in females than in males, except in the youngest and the oldest age groups. This sex difference was most pronounced within the oldest group of children, in which the difference was significant as regards free cholesterol.

The relative amounts of cholesterol and phosphatides seemed to be larger and the percentage of "total fatty acid" correspondingly lower in young women than in men of the same age. The differences were not significant, however, and within the other age groups there was no sex difference with regard to serum lipids.

Age (table 5).—Like other investigators, I found a lower serum cholesterol concentration in children than in adults, but the differences were not significant. There was no difference in serum cholesterol between the children of the oldest age group and young adults.

On the other hand, I found higher values for phospholipid and phosphatides in children than in adults, the difference being nearly three

20. Lundsteen, E., and Vermehren, E.: Compt. rend. d. trav. du lab. Carlsberg, série chim. **21**:147, 1936.

TABLE 1.—*Values for Serum Lipids in Normal Persons*

No.	Age	Index Constitution‡	Total Cholesterol, Mg./100 Cc.	Free Cholesterol, Mg./100 Cc.	Cholesterol Ester, Mg./100 Cc.	Free Cholesterol, % of Total	Total Lipids, Mg./100 Cc.	Phospholipid, Mg./100 Cc.	Phosphatides, Mg./100 Cc.	Total Fatty Acid, Mg./100 Cc.	Lipid Fractions, % Cholesterol	Phosphatides	Total Fatty Acid
Men Under 50 Years													
1	19	—1.17 L	183	56	127	30.6	700	5.6	140	377	26.1	20.0	53.9
2	20	—1.71 L	171	45	126	26.3	755	4.7	117.5	466.5	22.6	15.6	61.8
3	21	—1.55 L	142	32	110	22.5	505	6.0	150	213	28.1	29.7	42.2
4	21	—1.26 L	252	67	185	26.6	1,010	11.2	280	478	25.0	27.7	47.3
5	21	—1.39 L	173	43	130	24.9	665	5.6	140	352	26.0	21.1	52.9
6	21	—0.76 P	163	49	114	30.1	755	4.8	120	472	21.6	15.9	62.5
7	22	—1.51 L	187	48	139	25.7	740	6.9	172.5	380.5	25.3	23.3	51.4
8	22	—0.87 I	225	60	165	26.7	855	8.0	200	430	26.3	23.4	50.3
9	22	—0.86 I	187	49	138	26.2	765	8.3	207.5	370.5	24.4	27.1	48.4
10	22	—0.90 I	205	51	154	24.9	725	7.3	182.5	337.5	28.3	25.2	46.6
11	22	—0.52 P	204	51	153	25.0	735	6.5	162.5	368.5	27.8	22.1	50.1
12	23	—0.84 I	172	41	131	23.8	725	6.0	150	405	23.7	20.7	55.6
13	23	—0.48 P	167	39	128	23.4	625	6.4	160	296	26.7	25.6	47.7
14	23	—0.11 P	180	44	145	23.8	695	7.7	192.5	318.5	27.2	27.7	45.1
15	24	—0.78 I	198	40	158	20.2	720	6.0	150	372	27.5	20.8	51.7
16	24	—0.82 I	218	57	161	26.1	925	7.6	190	417	26.4	23.0	50.5
17	24	—0.72 I	167	40	127	24.0	595	4.2	105	323	28.1	17.6	54.3
18	25	—0.55 P	148	33	115	22.3	600	6.0	150	302	24.7	25.0	50.3
19	27	—0.66 I	199	64	135	32.2	...	...	...	...	....	....	....
20	27	—0.94 L	271	69	202	25.5	...	...	...	...	....	....	....
21	27	—1.51 L	216	55	161	25.5	...	...	...	...	....	....	....
22	27	—1.76 L	150	27	123	18.0	540	5.2	130	260	27.8	24.1	48.1
23	27	—1.82 L	135	26	109	19.3	525	4.6	115	275	25.7	21.9	52.4
24	27	+0.82 P	214	76	138	35.5	...	...	...	...	....	....	....
25	27	..	248	76	172	30.6	...	...	...	...	....	....	....
26	27	..	285	64	221	22.5	...	...	...	...	....	....	....
27	28	—0.83 I	162	38	124	23.5	590	4.6	115	313	27.5	19.5	53.1
28	29	—0.18 P	172	34	138	19.8	1,005	5.1	127.5	795.5	15.7	11.6	72.6
29*	29	0.00 P	266	58	208	21.8	1,000	8.8	220	574	25.1	20.8	54.2
30	30	..	196	50	146	25.5	...	...	...	...	....	....	....
31	32	—1.09 L	176	45	131	25.8	765	6.0	150	439	23.0	19.6	57.4
32	32	—1.35 L	177	39	138	22.0	805	6.7	167.5	550.5	19.8	18.7	61.5
33	32	—1.08 L	144	36	108	25.0	820	5.8	145	531	17.6	17.7	64.8
34	33	—0.50 I	173	30	143	17.3	765	6.2	155	437	22.6	20.2	57.1
35	34	—0.40 I	216	60	156	27.8	785	7.4	185	384	27.5	23.6	48.9
36	34	—0.40 I	252	65	187	25.8	750	6.0	150	348	33.6	20.0	46.4
37	34	—1.15 L	240	55	185	22.9	775	6.8	170	365	31.0	21.9	47.1
38*	34	+0.19 P	240	73	167	30.4	910	7.6	190	480	26.4	20.9	52.7
39†	34	..	222	58	164	26.1	690	5.9	147.5	320.5	32.2	21.4	46.4
40*	35	+0.80 P	248	57	191	23.0	810	7.2	180	382	30.6	22.2	47.2
41	36	—0.51 I	225	71	154	31.6	...	...	...	...	....	....	....
42	36	—0.90 L	210	54	156	25.7	...	...	...	...	....	....	....
43	37	—0.55 I	186	49	137	26.3	...	...	...	...	....	....	....
44	37	—0.15 P	201	50	151	24.9	1,065	7.0	175	679	19.1	16.6	64.4
45	37	—0.53 I	200	58	142	29.0	670	6.6	165	305	29.9	24.6	45.5
46	39	—0.67 L	237	69	168	29.1	780	5.4	135	408	30.4	17.3	52.3
47	39	..	276	83	193	30.1	975	9.8	245	454	28.3	25.1	46.6
48	40	—0.40 I	248	61	187	24.6	775	7.8	195	332	32.0	25.2	42.8
49	40	—0.40 I	213	66	147	31.0	820	5.6	140	467	26.0	17.1	57.0
50	40	..	168	43	125	25.6	915	6.3	157.5	589.5	18.4	17.2	64.4
51	41	—1.00 L	194	43	151	22.2	540	4.6	115	231	35.9	21.3	42.8
52*	41	+0.38 P	265	78	187	29.4	1,085	9.3	232.5	537.5	25.6	22.5	51.9
53	41	..	164	42	122	25.6	...	...	...	...	....	....	....
54	46	..	220	73	147	33.2	915	7.9	197.5	497.5	24.0	21.6	54.4
55†	36	..	....	..	....	....	920	6.3	170	...	....	18.5	....
56†	40	..	....	..	....	....	980	6.6	165	...	....	16.8	....
57†	41	..	....	..	....	....	900	6.4	160	...	....	18.0	....
58†	48	..	....	..	....	....	910	8.6	215	...	....	23.6	....
Men Over 50 Years													
1*	50	+0.20 I	222	59	163	26.6	835	6.7	167.5	445.5	26.6	20.1	53.4
2*†	50	..	....	..	....	....	870	5.6	140	...	....	16.1	....
3*†	50	..	225	54	171	24.0	1,000	8.6	215	620	21.2	20.3	58.5
4*†	50	..	197	54	143	27.4	1,025	8.8	220	608	19.2	21.5	59.3
5*	55	+0.55 P	181	45	136	24.9	755	5.6	140	434	24.0	18.5	57.5
6*†	58	..	....	..	....	....	780	5.9	147.5	...	....	18.9	....
7*	59	+0.04 I	241	69	172	28.6	805	9.1	227.5	336.5	29.9	28.3	41.8
8*†	60	..	....	..	....	....	940	6.2	155	...	....	16.5	....
9	60	..	297	97	200	32.7	...	...	...	...	....	....	....
10	61	—0.12 L	228	63	165	27.6	1,170	10.1	252.5	689.5	19.5	21.6	58.9
11	63	+0.89 P	293	88	205	30.0	1,080	7.9	197.5	539.5	28.4	19.2	52.4
12	69	..	240	62	178	25.8	1,090	8.8	220	630	22.0	20.2	57.8
13	70	+0.50 P	232	58	174	25.0	1,060	7.4	185	643	21.9	17.5	60.7
14	72	+1.01 P	290	73	217	25.2	1,380	10.2	255	835	21.0	18.5	60.5
15	72	+0.11 I	320	90	230	28.1	810	9.3	232.5	257.5	39.5	28.7	31.8
16	73	..	201	67	134	33.3	1,180	5.8	145	834	17.0	12.3	70.7
17	73	..	299	93	206	31.1	...	...	...	...	....	....	....

TABLE 1.—*Values for Serum Lipids in Normal Persons—Continued*

No.	Age	Index Constitution‡	Total Cholesterol, Mg./100 Cc.	Free Cholesterol, Mg./100 Cc.	Cholesterol Ester, Mg./100 Cc.	Free Cholesterol, % of Total	Total Lipids, Mg./100 Cc.	Phospholipid, Mg./100 Cc.	Phosphatides, Mg./100 Cc.	Total Fatty Acid, Mg./100 Cc.	Lipid Fractions, %		
											Cholesterol	Phosphatides	Total Fatty Acid
Men Over 50 Years—Continued													
18	74	+0.86 P	175	52	123	29.7	1,080	7.1	177.5	727.5	16.2	16.4	67.4
19	75	+0.08 I	268	64	204	23.9	705	7.6	190	247	38.0	27.0	35.0
20	76	+0.35 P	229	59	170	25.8	...	...	...	...	....	....	....
21	76	+0.66 P	317	88	229	27.8	1,345	11.1	277.5	750.5	23.6	20.6	55.8
22	76	−0.83 L	200	56	144	28.0	540	6.6	165	175	37.0	30.6	32.4
23	79	+0.38 P	290	77	213	26.6	940	5.8	145	505	30.9	15.4	53.7
24	80	+0.28 P	205	56	149	27.3	600	6.8	170	225	34.2	28.3	37.5
25	80	..	237	67	170	28.3	690	7.6	190	263	34.3	27.5	38.1
26	81	+0.51 P	144	29	115	20.1	725	5.5	137.5	443.5	19.9	19.0	61.2
27	81	+1.09 P	240	62	178	25.8	670	6.8	170	260	35.8	25.4	38.8
28	81	−0.49 L	227	52	175	22.9	565	7.3	182.5	185.5	38.2	30.7	31.2
29	82	−0.93 L	171	40	131	23.4	760	4.9	122.5	466.5	22.5	16.1	61.4
Women													
1	20	..	173	45	128	26.0	600	5.3	132.5	294.5	28.8	22.1	49.1
2	21	−0.26 P	155	28	127	18.1	360	2.2	55	150	43.1	15.3	41.7
3	23	..	236	64	172	27.1	775	8.0	200	339	30.5	25.8	43.7
4	23	−0.90 I	318	71	147	22.3	900	10.0	250	362	34.2	26.9	38.9
5	23	−1.29 L	206	52	151	25.6	715	6.3	157.5	354.5	28.4	22.0	49.6
6	24	−1.13 L	197	60	137	30.5	995	10.7	267.5	580.5	19.8	26.9	53.3
7	26	−0.26 P	262	54	208	20.6	885	9.2	230	393	29.6	26.0	44.4
8	26	+0.21 P	170	42	128	24.7	680	7.3	182.5	307.5	25.8	27.7	46.6
9	27	−0.90 I	154	38	116	24.7	765	7.5	187.5	423.5	20.1	24.5	55.4
10	28	−0.82 I	237	54	183	22.8	895	8.7	217.5	440.5	26.5	24.3	49.2
11	28	−0.60 P	247	66	181	26.7	770	7.2	180	343	32.1	23.4	44.5
12	29	..	235	60	175	25.5	680	6.2	155	290	34.6	22.8	42.6
13	30	..	165	42	123	25.5	...	...	...	...	....	....	....
14†	30	..	....	..	....	....	820	5.2	130	...	....	15.9	....
15	30	..	235	54	181	23.0	985	8.6	215	535	22.9	21.8	54.3
16	30	−0.11 P	210	54	156	25.7	715	7.1	177.5	327.5	29.4	24.8	45.8
17	32	−1.31 L	189	55	134	29.1	...	...	...	...	....	....	....
18	34	+0.29 P	250	65	185	26.0	895	9.4	235	410	27.9	26.3	45.8
19	35	−0.81 L	264	69	195	26.1	990	6.7	167.5	358.5	33.4	21.2	45.4
20	36	−0.55 I	285	86	199	30.2	...	...	...	...	....	....	....
21	36	..	267	74	193	27.7	...	...	...	...	....	....	....
22	38	−0.31 P	253	67	186	26.5	830	8.1	202.5	374.5	30.5	24.4	45.1
23	39	−0.94 L	233	62	171	26.6	715	7.7	192.5	289.5	32.6	26.9	40.5
1	63	..	249	68	181	27.3	...	...	...	...	....	....	....
2	65	..	253	75	178	29.6	...	...	...	...	....	....	....
3	72	−0.60 L	250	57	193	22.8	710	8.4	210	250	35.2	29.6	35.2
4	74	..	219	65	154	29.7	...	...	...	...	....	....	....
5	75	..	254	73	181	28.7	1,380	9.3	232.5	886.5	18.4	16.8	64.7
6	78	+0.37 P	289	77	212	26.6	1,220	10.6	265	666	23.7	21.7	54.6
7	80	−0.69 L	190	56	134	29.5	985	7.7	192.5	602.5	19.3	19.5	61.2
8	84	..	173	42	131	24.3	685	7.0	175	337	25.3	25.5	49.2
9	84	−1.42 L	163	42	121	25.8	745	6.2	155	427	21.9	20.8	57.3
10	85	..	294	82	212	27.9	1,160	9.9	247.5	618.5	25.3	21.3	53.3
11	86	−0.15 I	197	48	149	24.4	710	7.5	187.5	325.5	27.7	26.4	45.8
12	87	−0.88 L	266	65	201	24.4	1,110	9.2	230	614	24.0	20.7	55.3
13	92	−0.79 L	248	72	176	29.0	1,190	8.1	202.5	739.5	20.8	17.0	62.1
14	92	−0.07 P	252	63	189	25.0	995	8.1	202.5	540.5	25.3	20.4	54.3
15	96	..	233	64	169	27.5	915	7.9	197.5	484.5	25.5	21.6	53.0
Boys													
1	1	..	157	45	112	28.7	700	6.3	157.5	385.5	22.4	22.5	55.1
2	3	..	215	66	149	30.7	1,060	8.8	220	625	20.2	20.8	59.0
3	3	..	190	52	138	27.4	700	6.7	167.5	342.5	27.1	23.9	48.9
4	4	..	221	63	158	28.5	795	7.7	192.5	381.5	27.8	24.2	48.0
5	4	..	228	61	167	26.8	1,060	8.5	212.5	619.5	21.5	20.0	58.4
6	4	..	192	62	130	32.3	920	7.1	177.5	550.5	20.9	19.3	59.8
7	4	..	220	65	155	29.5	850	8.0	200	430	25.9	23.5	50.6
8	5	..	303	77	226	25.4	870	9.6	240	327	34.8	27.5	37.6
9	5	..	261	60	201	23.0	1,125	9.8	245	619	23.2	21.8	55.0
10	6	..	185	47	138	25.4	795	6.4	160	450	23.3	20.1	56.6
11	6	..	222	62	160	27.9	955	8.2	205	528	23.2	21.5	55.3
12	6	..	230	67	163	29.1	960	8.5	212.5	217.5	34.8	32.2	33.0
13	6	..	249	64	185	25.7	980	8.1	202.5	478.5	26.5	21.8	51.5
14	6	..	170	49	121	28.8	810	6.2	155	285	27.9	25.4	46.7
15	7	..	215	74	141	34.4	855	8.9	222.5	417.5	25.1	26.0	48.8
16	7	..	217	57	160	26.3	835	7.8	195	423	26.0	23.4	50.7
17	7	..	171	58	113	33.9	800	5.7	142.5	286.5	28.5	23.8	47.8
18	7	..	191	53	138	27.7	700	6.4	160	349	27.3	22.9	49.9
19	7	..	215	56	159	26.0	900	8.5	212.5	172.5	35.8	35.4	28.8
20	7	..	191	62	129	32.5	710	8.1	202.5	316.5	26.9	28.5	44.6
21	7	..	211	56	155	26.5	890	8.1	202.5	476.5	23.7	22.8	53.5
22	7	..	213	45	168	21.1	940	7.5	187.5	539.5	22.7	19.9	57.4
23	7	..	136	43	93	31.6	680	7.3	182.5	361.5	20.0	26.8	53.2
24	7	..	184	60	124	32.6	475	3.1	77.5	213.5	38.7	16.3	44.9

TABLE 1.—*Values for Serum Lipids in Normal Persons—Continued*

No.	Age	Index Constitution‡	Total Cholesterol, Mg./100 Cc.	Free Cholesterol, Mg./100 Cc.	Cholesterol Ester, Mg./100 Cc.	Free Cholesterol, % of Total	Total Lipids, Mg./100 Cc.	Phospholipid, Mg./100 Cc.	Phosphatides, Mg./100 Cc.	Total Fatty Acid, Mg./100 Cc.	Lipid Fractions, %		
											Cholesterol	Phosphatides	Total Fatty Acid
Boy—Continued													
25	8	..	210	66	144	31.4	880	9.0	225	445	23.9	25.6	50.6
26	8	..	199	45	154	22.6	830	7.5	187.5	443.5	24.0	22.6	53.4
27	8	..	223	59	164	26.5	810	8.3	207.5	379.5	27.5	25.6	46.9
28	8	..	162	45	117	27.8	390	5.8	145	83	41.5	37.2	21.3
29	9	..	182	59	123	32.4	715	9.5	237.5	295.5	25.5	33.2	41.3
30	9	..	208	54	154	26.0	720	7.1	177.5	334.5	28.9	24.7	46.5
31	9	..	166	49	117	29.5	755	6.8	170	419	22.0	22.5	55.5
32	9	..	190	46	144	24.2	825	7.4	185	450	23.0	22.4	54.5
33	9	..	253	70	183	27.7	910	7.8	195	462	27.8	21.4	50.8
34	9	..	236	59	177	25.0	920	8.2	205	479	25.7	22.3	52.1
35	9	..	176	45	131	25.6	655	7.2	180	299	26.9	27.5	45.6
36	10	..	218	60	158	27.5	625	8.1	202.5	204.5	34.9	32.4	32.7
37	10	..	238	64	174	26.9	905	10.4	260	467	24.7	26.9	48.4
38	10	..	212	54	158	25.5	890	7.1	177.5	500.5	23.8	19.9	56.2
39	10	..	167	37	130	22.2	645	5.4	135	343	25.9	20.9	53.2
40	10	..	166	42	124	25.3	710	6.2	155	389	23.4	21.8	54.8
41	10	..	132	39	93	29.5	570	6.2	155	283	23.2	27.2	49.6
42	11	..	214	57	157	26.6	890	8.3	207.5	468.5	24.0	23.3	52.6
43	11	..	189	46	143	24.3	930	8.1	202.5	538.5	20.3	21.8	57.9
44	11	..	180	51	129	28.3	715	6.7	167.5	367.5	25.2	23.4	51.4
45	11	..	152	41	111	27.0	630	6.5	162.5	315.5	24.1	25.8	50.1
46	11	..	165	44	121	26.7	500	5.9	147.5	187.5	33.0	29.5	37.5
47	11	..	225	58	167	25.8	935	8.5	212.5	497.5	24.1	22.7	53.2
48	12	..	190	49	141	25.8	770	6.3	157.5	422.5	24.7	20.5	54.9
49	12	..	210	57	153	27.1	825	8.3	207.5	407.5	25.5	25.2	49.4
50	12	..	190	44	146	23.2	820	5.9	147.5	482.5	23.2	18.0	58.8
51	14	..	225	59	166	26.2	985	8.0	200	510	24.1	21.4	54.5
Girls													
1	1	..	147	41	106	27.9	790	5.8	145	498	18.6	18.4	63.0
2	1	..	143	50	93	35.0	...	...	...	...	....	....	....
3	1	..	162	50	112	30.9	790	6.2	155	473	20.5	19.6	59.9
4	3	..	228	54	174	23.7	995	8.5	212.5	554.5	22.9	21.4	55.7
5	3	..	183	59	124	32.2	570	6.5	162.5	224.5	32.1	28.5	39.4
6	4	..	207	61	146	29.5	920	8.0	200	513	22.5	21.7	55.8
7	4	..	194	42	152	21.6	1,040	8.2	205	641	18.7	19.7	61.6
8	5	..	260	63	197	24.2	895	9.6	240	395	29.1	26.8	44.1
9	5	..	242	48	194	19.8	950	9.3	232.5	475.5	25.5	24.5	50.1
10	5	..	209	55	154	26.3	980	7.1	177.5	593.5	21.3	18.1	60.6
11	5	..	283	77	206	27.2	900	9.7	242.5	374.5	31.4	26.9	41.6
12	5	..	219	59	160	26.9	796	7.9	197.5	378.6	27.5	24.8	47.6
13	5	..	242	62	180	25.6	1,065	8.6	215	608	22.7	20.2	57.1
14	5	..	157	45	112	28.7	...	...	...	...	....	....	....
15	5	..	175	49	126	31.2	820	7.5	187.5	457.5	21.3	22.9	55.8
16	6	..	211	55	156	26.1	710	6.5	162.5	336.5	29.7	22.9	47.4
17	6	..	292	84	208	28.8	1,080	10.6	265	522	27.0	24.5	48.4
18	6	..	193	49	144	25.4	840	7.1	177.5	469.5	23.0	21.1	55.9
19	7	..	212	51	161	24.1	855	7.8	195	448	24.8	22.8	52.4
20	7	..	213	62	151	29.1	770	8.5	212.5	344.5	27.7	27.6	44.7
21	7	..	176	37	139	21.0	845	6.1	152.5	516.5	20.8	18.0	61.1
22	8	..	252	61	191	24.2	900	10.5	262.5	385.5	28.0	29.2	42.8
23	8	..	299	84	215	28.1	1,005	11.8	295	411	29.8	29.4	40.9
24	8	..	264	76	188	28.8	995	9.3	232.5	498.5	26.5	23.4	50.1
25	8	..	210	63	147	30.0	910	7.4	185	515	23.1	20.3	56.6
26	8	..	196	45	151	23.0	795	6.4	160	439	24.7	20.1	55.2
27	9	..	285	69	216	24.2	670	8.3	207.5	177.5	42.5	31.0	26.5
28	9	..	256	70	186	27.3	875	8.4	210	409	29.3	24.0	46.7
29	9	..	217	51	166	23.5	885	7.7	192.5	475.5	24.5	21.8	53.7
30	9	..	204	53	151	26.0	790	6.9	172.5	413.5	25.8	21.8	52.3
31	10	..	153	53	100	34.6	560	6.6	165	242	27.3	29.5	43.2
32	10	..	179	48	131	26.8	790	7.5	187.5	423.5	22.7	23.7	53.6
33	10	..	274	72	202	26.3	895	9.7	242.5	378.5	30.6	27.1	42.3
34	10	..	255	76	179	29.8	940	9.6	240	445	27.1	25.5	47.3
35	10	..	263	69	194	26.2	1,050	9.2	230	557	25.0	21.9	53.0
36	11	..	207	45	162	21.7	920	8.6	215	498	22.5	23.4	54.1
37	12	..	206	55	151	26.7	825	8.2	205	414	25.0	24.8	50.2
38	12	..	172	49	123	28.5	735	6.6	165	396	23.4	22.4	54.1
39	12	..	254	78	176	30.7	740	8.0	200	286	34.3	27.0	38.6
40	12	..	177	52	125	29.4	670	7.7	192.5	300.5	26.4	28.7	44.9
41	13	..	...	55	...	....	810	8.4	210	...	....	25.9	....
42	13	..	181	44	137	24.3	895	5.4	135	579	20.2	15.1	64.7
43	13	..	279	58	221	20.8	1,155	9.8	245	631	24.2	21.2	54.6
44	14	..	228	75	153	32.9	730	9.0	225	277	31.2	30.8	37.9
45	16	..	235	63	172	26.8	830	9.1	227.5	367.5	28.3	27.4	44.3

* Patients with sciatica.
† Patients with fractures occurring just before discharge.
‡ L indicates a person in the leptosomatic group; I, in the intermediate group; P, in the pyknic group.

TABLE 2.—*Values for Serum Lipids in Normal Subjects in Relation to Sex and Age*

Sex	Age, Years	Total Cholesterol, Mg./100 Cc.				Free Cholesterol, Mg./100 Cc.				Cholesterol Ester, Mg./100. Cc.				Free Cholesterol, % of Total				Total Lipids, Mg./100 Cc.				Phospholipid, Mg./100 Cc.			
		n*	m† ± c‡	σ§		n	m ± c	σ		n	m ± c	σ		n	m ± c	σ		n	m ± c	σ		n	m ± c	σ	
M	1- 7	24	207.7 ± 7.7	38		24	58.5 ± 1.8	8.8		24	149.2 ± 7.0	34		24	28.4 ± 0.9	4.3		24	805 ± 35	173		24	7.6 ± 0.27	1.30	
M	8-14	27	195.5 ± 6.7	35		27	51.8 ± 1.7	8.8		27	143.7 ± 3.3	17		27	26.5 ± 0.7	3.4		27	769 ± 30	157		27	7.4 ± 0.25	1.30	
All boys		51	201.3 ± 5.1	36		51	55.0 ± 1.2	9.2		51	146.3 ± 3.7	27		51	27.4 ± 0.5	3.9		51	786 ± 23	164		51	7.5 ± 0.18	1.27	
M	19-46	54	208.0 ± 5.8	42		54	52.6 ± 1.9	14.1		54	150.4 ± 4.3	32		54	25.7 ± 0.6	4.3		47	786 ± 28	164		47	6.6 ± 0.22	1.51	
M	50-82	26	237.3 ± 10.1	52		26	64.4 ± 3.3	16.6		26	172.9 ± 7.0	36		26	26.9 ± 0.7	3.5		26	902 ± 46	233		26	7.4 ± 0.34	1.71	
All men		80	214.1 ± 5.4	48		80	56.4 ± 1.8	15.9		80	157.7 ± 3.8	34		80	26.1 ± 0.5	4.0		73	827 ± 23	198		73	6.9 ± 0.18	1.59	
F	1- 7	21	207.0 ± 8.4	39		21	54.9 ± 2.5	11.3		21	152.1 ± 7.1	33		21	26.9 ± 0.9	4.1		19	874 ± 32	141		19	7.9 ± 0.29	1.24	
F	8-16	23	228.1 ± 9.3	45		24	61.0 ± 2.4	12.0		23	167.1 ± 7.3	35		23	27.0 ± 0.8	3.9		24	849 ± 30	146		24	8.3 ± 0.32	1.56	
All girls		44	218.0 ± 6.5	43		45	58.2 ± 1.8	11.8		44	159.8 ± 5.2	35		44	27.0 ± 0.6	3.8		43	860 ± 22	143		43	8.1 ± 0.23	1.49	
F	20-39	22	224.5 ± 10.6	50		22	57.4 ± 2.8	13.1		22	167.1 ± 8.3	39		22	25.5 ± 0.9	4.3		19	778 ± 37	163		19	7.4 ± 0.47	2.08	
F	63-96	15	235.3 ± 9.1	35		15	63.3 ± 3.1	12.2		15	172.0 ± 6.2	24		15	26.8 ± 0.9	3.6		12	964 ± 70	242		12	8.3 ± 0.38	1.33	
All women		37	228.9 ± 7.3	44		37	59.8 ± 2.1	12.9		37	169.1 ± 5.5	34		37	26.0 ± 0.7	4.1		31	858 ± 39	218		31	7.8 ± 0.31	1.71	
All children		95	209.0 ± 4.1	40		96	56.5 ± 1.1	10.6		95	152.5 ± 3.2	31		96	27.2 ± 0.4	3.9		94	820 ± 16	158		94	7.8 ± 0.14	1.33	
All adults		117	218.8 ± 4.4	47		117	57.5 ± 1.4	15.0		117	161.3 ± 3.2	34		117	26.1 ± 0.4	3.9		104	836 ± 20	204		104	7.2 ± 0.16	1.60	

* Number of observations.
† Mean.
‡ Mean error.
§ Standard deviation.

TABLE 3.—*Values for Serum Lipids in Normal Subjects in Relation to Sex and Age*

Sex	Age, Years	Phosphatides, Mg./100 Cc.				Total Fatty Acid, Mg./100 Cc.				Lipid Fractions, %											
										Cholesterol				Phosphatides				Total Fatty Acid			
		n*	m† ± c‡	σ§		n	m ± c	σ		n	m ± c	σ		n	m ± c	σ		n	m ± c	σ	
M	1- 7	24	189 ± 6.8	33		24	408 ± 27	134		24	26.4 ± 1.1	5.6		24	23.8 ± 0.9	4.5		24	49.8 ± 1.7	8.5	
M	8-14	27	186 ± 6.3	33		27	388 ± 21	111		27	26.0 ± 0.9	4.8		27	24.7 ± 0.9	4.5		27	49.4 ± 1.7	8.7	
All boys		51	187 ± 4.5	32		51	397 ± 17	122		51	26.2 ± 0.7	5.1		51	24.2 ± 0.7	4.7		51	49.6 ± 1.2	8.5	
M	19-46	47	166 ± 5.5	38		43	410 ± 18	118		43	26.1 ± 0.7	4.5		47	21.3 ± 0.6	4.2		43	52.4 ± 1.0	6.8	
M	50-82	26	186 ± 8.5	43		23	484 ± 44	214		23	27.0 ± 1.6	7.7		26	21.4 ± 1.1	5.5		23	51.1 ± 2.6	12.6	
All men		73	173 ± 4.5	40		66	436 ± 20	160		66	26.4 ± 0.7	5.8		73	21.3 ± 0.6	4.8		66	52.0 ± 1.1	9.0	
F	1- 7	19	197 ± 7.3	31		19	464 ± 24	104		19	24.6 ± 1.0	4.4		19	22.7 ± 1.0	4.2		19	52.7 ± 1.8	7.8	
F	8-16	24	208 ± 8.0	39		23	414 ± 24	116		23	27.1 ± 1.0	4.8		24	24.8 ± 0.8	3.9		23	48.2 ± 1.7	8.3	
All girls		43	203 ± 5.8	37		42	437 ± 17	111		42	25.9 ± 0.8	4.9		43	23.9 ± 0.6	4.0		42	50.2 ± 1.3	8.4	
F	20-39	19	186 ± 11.8	51		18	362 ± 21	88		18	29.5 ± 1.4	6.0		19	23.6 ± 0.8	3.6		18	45.4 ± 1.2	5.3	
F	63-96	12	208 ± 9.5	33		12	542 ± 53	185		12	24.4 ± 1.2	4.1		12	21.8 ± 1.3	4.5		12	53.8 ± 2.2	7.4	
All women		31	195 ± 7.8	43		30	434 ± 29	160		30	27.5 ± 1.0	5.7		31	22.9 ± 0.7	4.0		30	49.4 ± 1.2	6.8	
All children		94	195 ± 3.5	33		93	415 ± 12	118		93	26.1 ± 0.5	4.9		94	24.1 ± 0.4	4.3		93	49.9 ± 0.9	8.3	
All adults		104	180 ± 4.0	40		96	435 ± 16	160		96	26.7 ± 0.6	5.9		104	21.8 ± 0.4	4.5		96	51.2 ± 0.9	8.4	

* Number of observations.
† Mean.
‡ Mean error.
§ Standard deviation.

TABLE 4.—*Differences Among Serum Lipids in Different Groups of Normal Subjects*

Groups	Total Cholesterol, Mg./100 Cc.	Free Cholesterol, Mg./100 Cc.	Cholesterol Ester, Mg./100 Cc.	Free Cholesterol, % of Total	Total Lipids, Mg./100 Cc.	Phospholipid, Mg./100 Cc.	Phosphatides, Mg./100 Cc.	Total Fatty Acid, Mg./100 Cc.	Lipid Fractions, %		
									Cholesterol	Phosphatides	Total Fatty Acid
Girls and boys	16.7 ± 8.2	3.2 ± 2.2	13.5 ± 6.4	−0.4 ± 0.8	74 ± 32	0.6 ± 0.29	15 ± 7.3	40 ± 24	−0.3 ± 1.1	−0.3 ± 0.9	0.6 ± 1.8
Girls and boys, 8 years	32.6 ± 11.5	9.2 ± 2.9	23.4 ± 8.0	0.5 ± 1.1	80 ± 42	0.9 ± 0.41	22 ± 10.3	26 ± 32	1.1 ± 1.3	0.1 ± 1.2	−1.2 ± 2.4
Adults, female and male	14.8 ± 9.0	3.4 ± 2.8	11.4 ± 6.7	−0.1 ± 0.9	31 ± 45	0.9 ± 0.36	22 ± 9.0	−2 ± 35	1.1 ± 1.2	1.6 ± 0.9	−2.6 ± 1.6
Adults, 50 years	21.5 ± 11.6	4.8 ± 3.4	16.7 ± 9.3	−0.2 ± 1.1	−8 ± 44	0.8 ± 0.52	20 ± 13.0	−48 ± 28	3.4 ± 1.6	2.3 ± 1.0	−6.0 ± 2.2
Adults and children	9.8 ± 6.1	1.0 ± 1.8	8.8 ± 4.5	−1.1 ± 0.6	16 ± 26	−0.6 ± 0.21	−15 ± 5.3	20 ± 20	0.6 ± 0.8	−2.3 ± 0.6	1.3 ± 1.3
Males											
Older adults and young children	−12.2 ± 10.2	−6.7 ± 2.5	−5.5 ± 7.7	−1.9 ± 1.1	−36 ± 46	−0.2 ± 0.37	−5 ± 9.3	−20 ± 34	−0.4 ± 1.4	0.9 ± 1.3	−0.4 ± 2.4
Young adults and older children	7.5 ± 8.9	0.8 ± 2.5	6.7 ± 5.4	−0.8 ± 0.9	17 ± 38	−0.8 ± 0.33	−20 ± 8.3	22 ± 28	0.1 ± 1.1	−3.4 ± 1.1	3.0 ± 2.0
Older and young adults	34.3 ± 11.7	11.8 ± 3.8	22.5 ± 8.2	1.2 ± 0.9	116 ± 51	0.8 ± 0.41	20 ± 10.3	74 ± 48	0.9 ± 1.7	0.1 ± 1.3	−1.3 ± 2.8
Females											
Older and young children	21.1 ± 12.5	6.1 ± 3.5	15.0 ± 10.2	0.1 ± 1.2	−25 ± 44	0.4 ± 0.43	10 ± 10.8	−50 ± 34	2.5 ± 1.4	2.1 ± 1.3	−4.5 ± 2.5
Young adults and older children	−3.6 ± 14.1	−3.6 ± 3.7	0 ± 11.1	−1.5 ± 1.2	−71 ± 48	−0.9 ± 0.57	−22 ± 14.3	−52 ± 32	2.4 ± 1.7	−1.2 ± 1.1	−1.8 ± 2.0
Older and young adults	10.8 ± 14.0	5.9 ± 4.2	4.9 ± 10.4	1.3 ± 1.3	206 ± 79	0.9 ± 0.00	22 ± 15.0	180 ± 57	−5.1 ± 1.8	−1.8 ± 1.5	7.4 ± 2.5

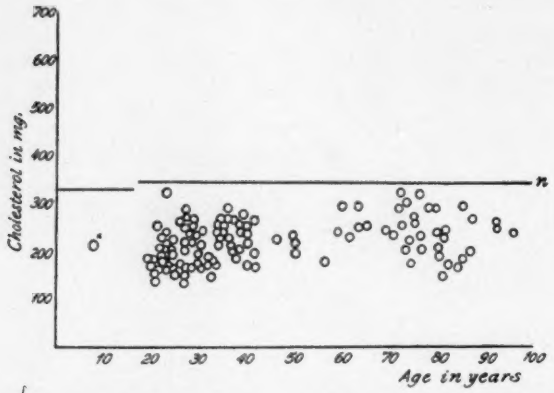

Fig. 1.—Relation between total cholesterol level and age. Line *n* indicates the upper normal limit; O^{x}, the mean value for 95 children. The illustrations have been previously published in Kornerup, V.: Familiær hypercholesterolæmi og xanthomatose, Kolding, Denmark, Konrad Jørgensen, 1948. The publisher has granted permission for their reproduction.

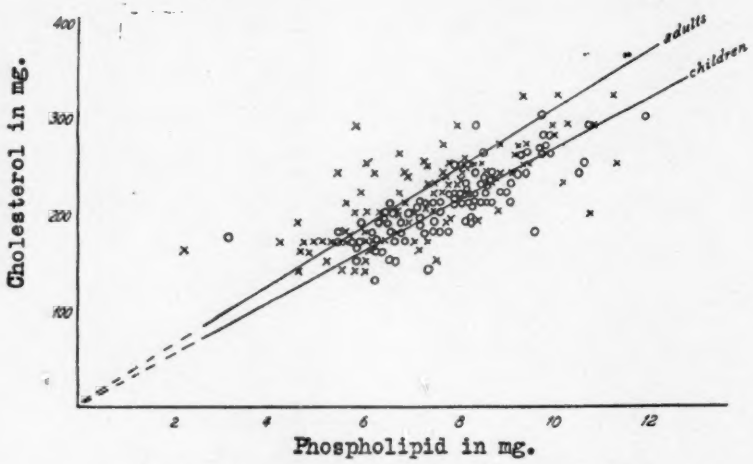

Fig. 2.—Relation between total cholesterol and phospholipid levels in serum of normal human beings. The crosses represent adults; the circles, children.

times the standard error. There was also found a significantly larger amount of serum phosphatides in children than in adults. Both in adults and in children there was proportionality between the different lipid values and between the values for total cholesterol and phosphatides (fig. 2). The values for serum lipids were surprisingly high in children. Possibly the explanation is that food of Danish children is rich in animal fat. During the war all school children got at least 0.5 liter of milk a day, secured by a practically compulsory lunch at school. The food of adults was relatively poor in animal fats during the war.

In accordance with other investigators, I found a tendency toward a higher concentration of serum lipids in elderly men than in young men; the difference, however, was significant only as regards free cholesterol.

The group of elderly women was too small to show anything regarding the relation of serum lipid concentration to age. No significant

TABLE 5.—*Average Values for Serum Lipids in the Entire Series of Normal Subjects*

	Total Cholesterol		Free Cholesterol		Total Lipids		Phospholipid	
	Adults	Children	Adults	Children	Adults	Children	Adults	Children
Mg./100 cc.	218.8	209.0	57.5	56.5	836	820	7.2	7.8
Mean error	± 4.4	± 4.1	± 1.4	± 1.1	± 20	± 16	± 0.16	± 0.14
Standard deviation	47	40	15.0	10.6	204	158	1.60	1.33

differences were found between the values in elderly and in young women, except as regards those for "total fatty acid."

Type of Constitution.—Each adult group was divided into three subgroups according to constitutional type, as follows: (1) chiefly leptosomatic, (2) intermediary and (3) chiefly pyknic.

The constitution is rarely quite pure, but generally a mixture of leptosomatic and pyknic properties in varying proportions. The terms leptomorphic and pyknomorphic were used by Conrad [21] in referring to the subjects belonging to subgroups 1 and 3 respectively.

The descriptions of the different types of body and the distinction between them being extremely subjective and arbitrary, various investigators have tried to construct anthropometric indexes on the basis of the relations between the different physical measures. Several indexes of this kind exist.

The index constructed by Strömgren,[22] based on the following measurements, is used in the present work:

1. Height, *a*.

21. Conrad, K.: Der Konstitutionstypus als genetisches Problem, Julius Springer, Berlin, 1941.

22. Strömgren, E.: Ztschr. f. Neurol. **159**:75, 1937.

2. Width of chest, *b*, i. e., the largest transverse diameter in the horizontal plane in which the depth of chest was measured. It is measured over the ribs at moderate inspiration (Martin's measurement no. 36).

3. Depth of chest, *c*, i. e., the distance between the lower border of the sternum and the end of the spinous process of the vertebra situated in almost the same

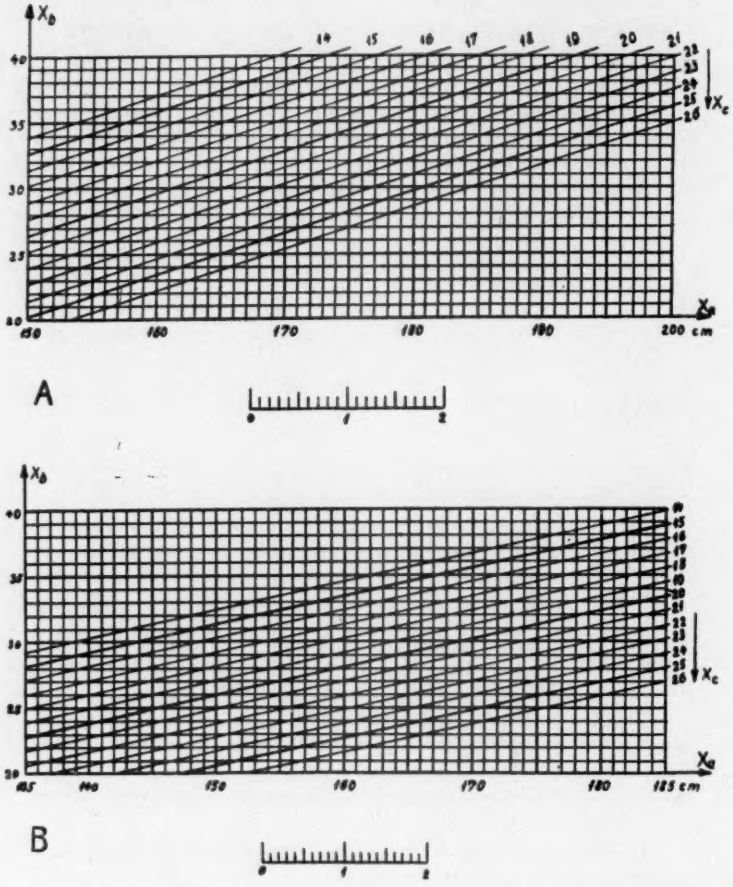

Fig. 3.—Strömgren's index diagram. *A*, for men; *B*, for women. Published with permission of Prof. E. Strömgren.

horizontal plane as the anterior point of measure, at moderate inspiration (Martin's measurement no. 37 [23]).

23. Martin, R.: Lehrbuch der Anthropologie, Jena, Gustav Fischer, 1928, vol. 1.

Width and depth of chest are measured with an ordinary pelvimeter with an accuracy of 0.5 cm. Strömgren's index is calculated from these three measurements by means of Strömgren's diagrams, which represent a kind of coordinate system of three dimensions. One has been constructed for men and one for women (fig. 3).

In the coordinate system the point (a,b) is found which corresponds to the determined height (a) and the width of the chest (b). Next, the distance to the oblique line, marked by the figure corresponding to the depth of chest (c), is measured with compasses. This distance, that is, the rectangular distance from the point (a, b) down to the line (c), is found on the scale given below the coordinate system. This measure is the index, which is regarded as positive when the point (a, b) lies above the oblique line (c) and negative when it lies below this line.

The table of indexes was in Strömgren's original work (1937), constructed in such a manner that definite leptosomatic types had an index of < -0.15 and definite pyknic types an index of $> +0.15$.

In a subsequent work (1942), Strömgren [24] himself stated that the zero line must be shifted in the negative direction, being placed at about -0.40.

This index has the disadvantage of indicating only the part of the constitution mainly related to the skeletal structure; it completely disregards the psyche. On the other hand, it is an advantage to have to deal with physical measurements only.

After having worked for some time with Strömgren's index, I realized that it could be used satisfactorily only if a correction for age were made.

In figure 4, 193 index values are correlated with individual ages. The values were obtained from 112 males and 81 females, fairly equally distributed from 17 to 92 years.

Figure 4 shows a marked correlation between index and age. The index seems to change with increasing years, following a natural logarithmic curve. However, by dividing the material in two age groups below and above 50, it is possible to indicate the approximate relation between age and index with straight lines.

In the group below 50 the line may be expressed by the equation:

$$i = k_1 + k_2 a$$

where i is the index and a the age.

The following equations indicate the calculation of k_1 and k_2, where n is the number of observations and Σ the sign of summation:

$$k_1 n + k_2 \Sigma a = \Sigma i$$

and

$$k_1 \Sigma a + k_2 \Sigma a^2 = \Sigma ai$$

These (2) equations are solved with regard to k_1 and k_2.

In computing the index for the group above 50 a certain change of the index in relation to age is disregarded and the straight line may be expressed by the equation:

$$i = k_3$$

where k_3 is the mean of the indexes.

Whereas Strömgren used only the lines $i = -0.40 \pm 0.15$ for classification of an index-determined series of males and females in a leptosomatic, an intermediary and a pyknic group, the present classification, owing to the change of

24. Strömgren, E.: Nord. med. **13**:157, 1942.

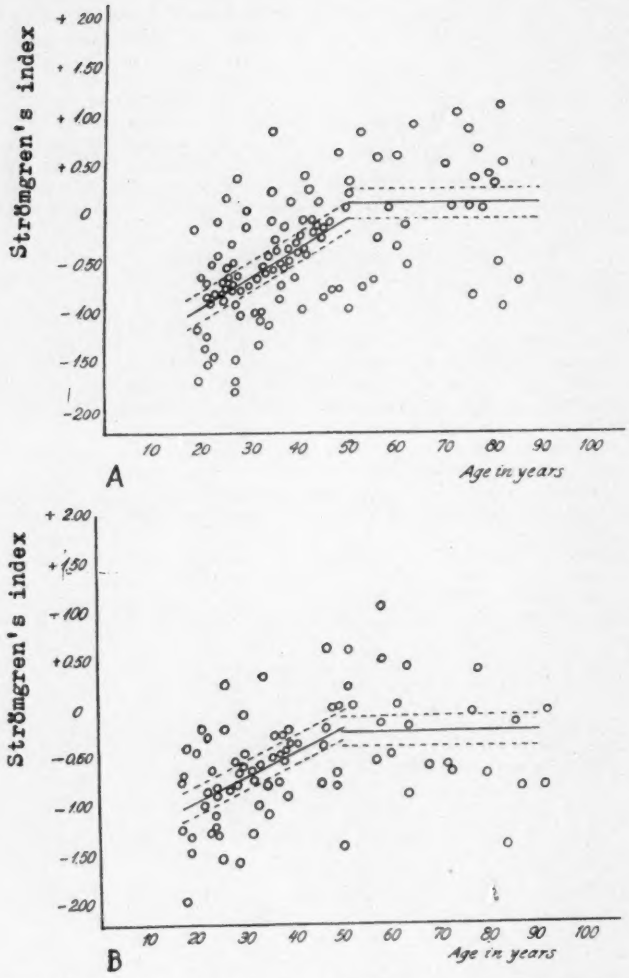

Fig. 4.—Relation between Strömgren's index and age. *A*, for male subjects; *B*, for females.

the index with increasing years under the age of 50, is based on the lines $i = k_1 \pm 0.15 + k_2\ a$, where k_1 and k_2 have been calculated as indicated and separately for each sex.

For the 81 males under 50 years of age represented in figure 4 *A* the equation for this line becomes $i = -1.59 + 0.031\ a$. The zone of

$$i = -1.59 \pm 0.15 + 0.031\ a$$

has been used as a basis for classification of the entire series of males under 50 years of age in a leptosomatic, an intermediary and a pyknic group, dependent on whether the index is under, in or over this zone.

For the 34 males over 50 years of age represented in figure 4 *A* the intermediary zone is represented by

$$i = +0.09 \pm 0.15$$

For the 57 females under 50 years of age represented in figure 4 *B* the intermediary zone is

$$i = -1.48 \pm 0.15 + 0.025\ a$$

and for the 36 women over 50 years of age represented in figure 4 *B* the zone is

$$i = -0.28 \pm 0.15$$

These relations between age and index have been tabulated in table 7. Subjects for whom indexes have been determined previously can, by means of this table, be classed in a leptosomatic, an intermediary and a pyknic group.

After the introduction of this correction of the zero of Strömgren's index for age there is, with very few exceptions, a fair accordance between the measured physical constitution and the subjective somatoscopic estimate.

Data on the normal series divided on this principle are given in table 6. Like other investigators I found a tendency toward higher serum lipid values in pyknic than in leptosomatic subjects, whereas those of the intermediary group generally lie in between. There are, however, no significant differences.

The relations of the different lipid fractions were the same for all the groups examined.

The higher serum lipid values in the group of elderly subjects may perhaps be due to the presence of pyknic subjects in this group, because pyknic subjects particularly tend to rising serum lipid values with increasing age. The 13 elderly pyknic subjects had an average total cholesterol value of 241.3 mg. per hundred cubic centimeters. The number of subjects was too small for definite conclusions to be drawn. Latent diseases apt to occur in pyknic types, such as arteriosclerosis, may possibly play a part, these diseases being in part diseases of old age which occur in pyknic subjects when they are relatively young.

The groups were too small for the differences in the serum lipids between the pyknic and the leptosomatic subjects to be significant, but there seemed to be a parallelism between the serum lipid values and the constitutional type of the three groups.

TABLE 6.—*Values for Serum Lipids in Normal Subjects in Relation to Type of Constitution*

	Leptosomatic Subjects							Subjects in Intermediary Group				Pyknic Subjects							Difference in Serum Lipids between Pyknic and Leptosomatic Subjects
	Young		Elderly		Total							Young		Elderly		Total			
	n*	m†	n	m	n	m ± ε‡	σ§	n	m ± ε	σ		n	m	n	m	n	m ± ε	σ	
Total cholesterol, mg./100 cc.	22	197.4	9	215.9	31	202.8 ± 7.1	40	26	218.8 ± 9.9	50		19	211.8	13	241.3	32	223.8 ± 8.8	50	21.0 ± 11.3
Free cholesterol, mg./100 cc.	22	50.3	9	55.9	31	51.9 ± 2.3	12.6	26	56.9 ± 2.8	14.5		19	58.6	13	63.7	32	57.7 ± 2.8	16.1	5.8 ± 3.6
Cholesterol ester, mg./100 cc.	22	147	9	160	31	151 ± 5.9	33	26	162 ± 6.7	34		19	158	13	178	32	166 ± 7.2	41	15 ± 9.3
Free cholesterol, % of total	22	25.3	9	25.9	31	25.4 ± 0.7	4.0	26	25.9 ± 0.7	3.8		19	25.1	13	26.1	32	25.5 ± 0.7	4.1	0.1 ± 1.0
Total lipids mg./100 cc.	18	735	9	867	27	779 ± 39	208	22	765 ± 23	109		18	805	12	984	30	876 ± 44	242	97 ± 59
Phospholipid, mg./100 cc.	18	6.5	9	7.6	27	6.9 ± 0.33	1.72	22	7.2 ± 0.30	1.42		18	7.0	12	7.7	30	7.3 ± 0.25	1.90	0.4 ± 0.48
Total fatty acid, mg./100 cc.	18	381	9	461	27	408 ± 29	153	22	367 ± 14	65		18	417	12	547	30	469 ± 33	179	61 ± 44
Lipid fractions, % cholesterol	18	26.6	9	26.5	27	26.6 ± 1.1	5.9	22	28.5 ± 1.1	5.4		18	27.2	12	25.4	30	26.5 ± 1.1	6.0	−0.1 ± 1.6
Phosphatides	18	22.0	9	23.0	27	22.4 ± 1.0	5.1	22	23.4 ± 0.7	3.5		18	22.2	12	20.1	30	21.3 ± 0.8	4.6	−1.1 ± 1.3
Total fatty acid	18	51.4	9	50.6	27	51.1 ± 1.7	8.8	22	48.2 ± 1.5	6.8		18	50.7	12	54.6	30	52.2 ± 1.7	9.2	1.1 ± 2.4

* Number of observations.
† Mean.
‡ Mean error.
§ Standard deviation.

SUMMARY AND CONCLUSIONS

The anthropologic index calculated after Strömgren varied in the present material with increasing years up to the age of 50. The relation between age and index in the material was tabulated (table 7). By means of this table any series of subjects measured may be divided into three groups, one chiefly leptosomatic, one intermediary and one chiefly pyknic.

TABLE 7.—*Relation Between Ages and Strömgren's Index*

Age, Years	Males		Females	
	Index*	Intermediary Limit	Index	Intermediary Limit
17	−1.06	−1.21- −0.91	−1.05	−1.20- −0.90
18	−1.06	−1.18- −0.88	−1.03	−1.18- −0.88
19	−1.00	−1.15- −0.85	−1.00	−1.15- −0.85
20	−0.97	−1.12- −0.82	−0.98	−1.13- −0.83
21	−0.94	−1.09- −0.79	−0.95	−1.10- −0.80
22	−0.91	−1.06- −0.76	−0.93	−1.08- −0.78
23	−0.88	−1.03- −0.73	−0.90	−1.05- −0.75
24	−0.85	−1.00- −0.70	−0.88	−1.03- −0.73
25	−0.82	−0.97- −0.67	−0.85	−1.00- −0.70
26	−0.79	−0.94- −0.64	−0.83	−0.98- −0.68
27	−0.76	−0.91- −0.61	−0.80	−0.95- −0.65
28	−0.73	−0.88- −0.58	−0.78	−0.93- −0.63
29	−0.69	−0.84- −0.54	−0.75	−0.90- −0.60
30	−0.66	−0.81- −0.51	−0.73	−0.88- −0.58
31	−0.63	−0.78- −0.48	−0.70	−0.85- −0.55
32	−0.60	−0.75- −0.45	−0.68	−0.83- −0.53
33	−0.57	−0.72- −0.42	−0.66	−0.81- −0.51
34	−0.54	−0.69- −0.39	−0.63	−0.78- −0.48
35	−0.51	−0.66- −0.36	−0.61	−0.76- −0.46
36	−0.48	−0.63- −0.33	−0.58	−0.73- −0.43
37	−0.45	−0.60- −0.30	−0.56	−0.71- −0.41
38	−0.41	−0.56- −0.26	−0.53	−0.68- −0.38
39	−0.38	−0.53- −0.23	−0.50	−0.65- −0.35
40	−0.35	−0.50- −0.20	−0.48	−0.63- −0.33
41	−0.32	−0.47- −0.17	−0.46	−0.61- −0.31
42	−0.29	−0.44- −0.14	−0.43	−0.58- −0.28
43	−0.26	−0.41- −0.11	−0.41	−0.56- −0.26
44	−0.23	−0.38- −0.08	−0.38	−0.53- −0.23
45	−0.20	−0.35- −0.05	−0.35	−0.50- −0.20
46	−0.16	−0.31- −0.01	−0.33	−0.48- −0.18
47	−0.13	−0.28- +0.02	−0.30	−0.45- −0.15
48	−0.10	−0.25- +0.05	−0.28	−0.43- −0.13
49	−0.07	−0.22- +0.08	−0.26	−0.41- −0.11
≦50	+0.09	−0.06- +0.24	−0.28	−0.43- −0.13

* Index values under the intermediary limit indicate leptosomatic persons and those over the intermediary limit indicate pyknic types.

The absolute and relative amounts of phospholipid and phosphatides in serum are larger in children than in adults.

In conformity with other investigators I found a tendency toward higher serum lipid values in females than in males, in elderly than in young persons and in pyknic than in leptosomatic types. In children I found a tendency toward lower cholesterol concentration in serum. The differences, however, were small and, as a rule, not significant.

That elderly normal subjects present higher serum lipid values than young normal subjects may possibly be due to the presence of latent characteristic morbid alterations in pyknic subjects of this age group.

LOWER NEPHRON NEPHROSIS

Report of Treatment of Forty-Four Patients by Repeated Replacement Transfusions

J. DAUSSET, M.D.
PARIS, FRANCE

TWO THERAPEUTIC methods were recently recommended for the treatment of patients with acute azotemia, utilizing dialysis to remove nitrogenous waste from the blood. The machine which performs dialysis through cellophane® tubing (the artificial kidney) was invented in Holland by Kolff [1] and independently in Canada by Murray and others.[2] Dialysis of nitrogenous waste through peritoneal membrane (peritoneal irrigation) was used successfully in human beings by Fine, Frank and Seligman.[3]

These methods, though brilliant, do not entirely solve the problem. The use of replacement transfusion, with or without the additional aid of various methods of dialysis, has in my experience proved of more value in these cases.

Abbel, Rowntree and Turner [3a] employed plasmapheresis in animals. Gilbert and Tzanck [3b] used the same technic in patients with uremia, twenty-five years ago, in 1925.

Replacement transfusion was carried out experimentally in dogs by Tzanck, Bessis and Burstein.[4] It was proposed as a treatment of

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From the National Tranfusion Center 53, Boulevard Diderot.

Fellow in the United States of America of the Cultural Relations Department, French Foreign Ministry.

1. Kolff, W. J., and Berck, H. T. J.: The Artificial Kidney: A Dialyser with a Great Area, Acta med. Scandinav. **117**:121, 1944; New Ways of Treating Uraemia: The Artificial Kidney, Peritoneal Lavage, Intestinal Lavage, London, J. & A. Churchill, Ltd., 1947.

2. Murray, G.: Development of an Artificial Kidney, Arch. Surg. **55**:505, (Nov.) 1947. Murray, G.; Delorme, E., and Thomas, N.: Artificial Kidney, J. A. M. A. **137**:1596 (Aug. 28) 1948.

3. Fine, J.; Frank, M. A., and Seligman, A. M.: The Treatment of Acute Renal Failure by Peritoneal Irrigation, Ann. Surg. **124**:857, 1946.

3a. Abbel, J. J.; Rowntree, L. G., and Turner, B. B.: Plasma Removal with Return of Corpuscles (Plasmaphaeresis), J. Pharmacol. & Exper. Therap. **5**:625, 1913-1914.

3b. Gilbert, A., and Tzanck, A.: Emission sanguine avec restitution globulaire (traitement des néphrites chroniques avec ozotémie et anémie), Bull. et mém. Soc. méd. d. hôp. de Paris **49**:40, 1925.

4. Tzanck, A.; Bessis, M., and Burstein, M.: Recherches sur le remplacement du sang circulant par du sang frais, du sang conservé et du plasma, Compt. rend. Acad. sc. **222**:822, 1946.

erythroblastosis fetalis almost simultaneously by Bessis,[5] by Wiener and Wexler[6] and by Wallerstein.[7] Bessis and Bernard[8] suggested its use as a treatment in several diseases and types of intoxication, in the acute azotemia of lower nephron nephrosis. Bessis and Bernard[9] extended its indications to the treatment of children and adults with acute leukemia.

The first patients with nephrosis and associated anuria treated by this method were those of Tzanck and Dausset.[10] Pasteur Vallery-Radot and his associates[11] subsequently used this method with success in the treatment of 1 patient. Derot and others[12] and I[13] then successfully combined replacement transfusion and peritoneal irrigation in the treatment of several additional patients.

Several other cases have been published since.[14]

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5. Bessis, M.: Traitement de la maladie hémolytique du nouveau-né, Gynécologie, **113**:45, 1946.

6. Wiener, A. S., and Wexler, I. B.: The Use of Heparin when Performing Exchange Blood Transfusions in New Born Infants, J. Lab. & Clin. Med. **31**:1016, 1946.

7. Wallerstein, H.: Treatment of Severe Erythroblastosis by Simultaneous Removal and Replacement of the Blood of the Newborn Infant, Science **103**:583, 1946.

8. Bessis, M., and Bernard, J.: Les indications de l'exsanguino-transfusion en dehors de la maladie hémolytique du nouveau-né, Sang **19**:40, 1948. Bessis, M.: La substitution sanguine appliquée a la recherche médicale, Rev. d'hémat. **3**:230, 1948; The Use of Replacement Transfusion in Diseases Other Than Hemolytic Disease of the Newborn, Blood **4**:324, 1949.

9. Bessis, M., and Bernard, J.: Remarquables résultats du traitement par l'exsanguino-transfusion d'un cas de leucémie aiguë, Bull. et mém. Soc. méd. d. hôp. de Paris **63**:871, 1947.

10. Tzanck, A., and Dausset, J.: L'exsanguino-transfusion dans les anuries, Bull. et Mém. Soc. méd. d. hôp. de Paris **64**:563, 1948.

11. Pasteur Vallery-Radot; Milliez, P.; Laroche, C.; Lhermitte, F., and Levasseur, C.: Première observation de néphrite aiguë azotémique indiscutablement guérie par la méthode de Bessis, Bull. et mém. Soc. méd. d. hôp. d. Paris **64**:908, 1948.

12. Derot, M.; Tanret, P.; Solignac, H., and Delaveau, P.: Hépato-néphrite hémolytique après ingestion accidentelle de chlorate dt sodium: Guérison par la dialyse péritonéale et l'exsanguino-transfusion, Bull. et mém. Soc. méd. d. hôp. de Paris **64**:1062, 1948.

13. Dausset, J.: Le problème de l'azotémie aiguë: Son traitement comparé par l'exsanguino-transfusion et les méthodes de dialyse, Mémoire pour le concours de Médaille d'Or (Assistance Publique de Paris), November 1948.

14. Lian, C.; Siguier, F.; Crosnier, J.; Savoie, J. C., and Poullain, P.: Anurie "post-abortum," due au bacille "perfringens," guérie par exsanguino-transfusion, Bull. et mem. Soc. méd. d. hôp. de Paris **65**:265, 1949. Lian, C.; Siguier, F., and Crosnier, J.: Valeur des exsanguino-transfusions dans le traitement de certaines anuries à bacille "perfringens," ibid. **65**:272, 1949. Tzanck, A.; Baumann, J.; Bessis, M., and Giraud: Le triple probleme thérapeutique de la septicémie à "perfringens" post-abortum à propos d'un cas traité par hystérectomie et ex-sanguino-transfusions répétées, Mém. Acad. de chir. **75**:132, 1949.

The method [15] consists principally in removing from the body the blood that contains toxic substances and substituting normal blood taken from several donors. As the operation requires simultaneously both transfusion and exsanguination, it produces a more and more effective dilution which leads at last to almost complete replacement of the blood. As the normal blood comes in the nonprotein nitrogen, a most diffusible substance, gradually passes over from the tissues into the blood stream and is partly eliminated by exsanguination. Therefore the quantity of blood injected and removed is important. Sometimes a single operation is sufficient, but more frequently it is neccessary to repeat the replacement transfusion in order to help the body eliminate the products of daily ureogenesis while awaiting the spontaneous functional recovery of the kidneys. The resumption of urinery output appears from the tenth to the seventeenth day. The purpose of the replacement transfusion is to help the patient overcome this period of renal failure.

In many cases lower nephron nephrosis is due to massive hemolysis of blood and/or to passage into the blood stream of the heme pigments (hemoglobin, myohemoglobin and methemoglobin). The replacement transfusion removes these nondialyzable pigments from the blood stream. Replacement transfusion also removes toxic substances present in the blood stream after criminal or accidental poisoning.

TECHNIC

The replacement transfusion in itself is a simple operation, but it nevertheless requires careful preparation in order to avoid serologic errors. The study of the recipient's blood should include typing in the Landsteiner system and the standard Rh system and systematic testing for irregular agglutinins, complete and incomplete; the typing of donors must be done carefully, and their blood should be cross matched with that of the recipient. In theory, replacement transfusion should be made only with blood compatible in the Landsteiner system and in Rh factor, but it is in fact possible to use great quantities of type O blood in patients with blood of type A, B or AB when A and B substances (the so-called Witebski substances) are added.

The blood should be as fresh as possible, though experience has proved that banked blood may be used provided it has not been stored for longer than a week. However, fresh blood stored twenty-four or forty-eight hours should be used predominantly. The blood bank system offers the greatest facilities for obtaining the required quantity of blood of the proper type in a short time. Blood may be collected as in the usual banking technic. The use of sodium citrate must be limited to a minimum.

The patient should be prepared half an hour before the operation with an injection of 0.01 Gm. of morphine sulfate and should be given 1 to 5 Gm. of calcium

15. Tzanck, A., and Bessis, M.: La substitution sanguine par l'exsanguino-transfusion, Presse méd. **31**:376, 1948.

gluconate during the procedure, in order to prevent tetany, which may be caused by sodium citrate.

Injection of the blood is done in most cases as in the usual indirect transfusion (fig. 1). The blood flows by gravity from the bottle into the recipient's body through pyrogen-free tubing. I recommend the use of a large size needle (15 gage in the adult), so that the blood flows very freely. Exsanguination is the difficult part of the operation. If the venous network of the patient is well developed

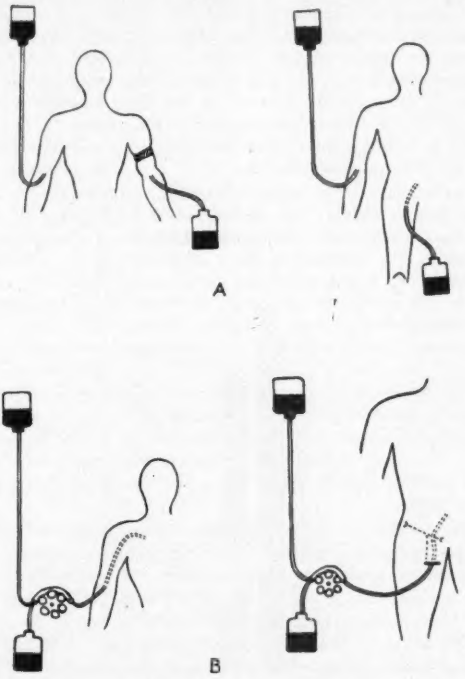

Fig. 1.—Replacement transfusion. *A*, by two routes; *B*, by one route.

a second needle, as large as the first and coated with silicon or paraffin, should be used. It is best to introduce this needle with the point heading distally into the largest vein available in the extremity opposite that used for the transfusion. The flow of blood is freer when the needle point is at a venous junction.

When a needle is used the administration of heparin (2 mg. per kilogram of body weight) is required to prevent clotting in the system. This substance, when it is given intravenously in two doses, half at the beginning and half midway in the operation, is entirely safe. When a catheter of polyvinyl is used in place of a metal needle, only 1 mg. of heparin per kilogram, or none, is needed. This

catheter is a supple and translucent tube with an inside diameter of 0.047 inch 1.2 mm.) and an outside diameter of 0.067 (1.7 mm.), which causes little damage to the endothelium of the vein and has been biologically tested for this purpose. It should be sterilized by immersion in benzalkonium chloride (zephiran chloride®) for an hour and washed in sterile saline solution immediately before use. Such a catheter may be introduced through the lumen of the needle and pushed forward to a large vessel in which the circulation is rapid enough to prevent clotting at the extremity of the catheter, but I prefer in most instances to use an incision in the short saphenous vein on the level femoral triangle. In this case the line of incision is perpendicular and medial to the course of the femoral artery, 10 to 15 cm. below Poupart's ligament. From this point of entrance into the saphenous vein the catheter need be inserted only a distance of 4.0 to 6.0 cm. to reach the large femoral vein, but it is usually pushed forward 15 or 20 cm. into the iliac vein. The advantage in the use of the short saphenous vein lies in the possibility it offers for an eventual repetition of the operation. The second time it is sufficient to introduce the catheter through the same hole or just above the ligature of the previous exsanguination.

In addition to the existing venous pressure, force is always needed to insure an active outflow of blood. This can be provided by gravity alone, with the heparinized blood flowing freely down into a bottle placed beneath the level of the patient; however, it is preferable to use a more active force. Negative pressure can be employed. A simple transfusion pump, either electric or hand operated, has also been found useful. The use of the tourniquet should be limited to patients in whom exsanguination is done through a needle in the antecubital area. A tourniquet produces pain if used too long; its use should be avoided as often as possible.

Dausset and Moulinier[16] described a method of replacement transfusion using only one vein for the infusion and the removal of the blood: A polyvinyl catheter is inserted as far as possible into a large venous trunk (either the brachiocephalic or the iliac vein). A special pump capable of producing controlled alternate positive and negative pressure easily allows the injection and removal of blood from the one vessel.

During the procedure the intake and output of blood should be exactly balanced to avoid fluctuations exceeding 10 per cent of the total blood volume of the patient. This amount can be assumed to be approximately 500 cc. in the average adult. However, at the beginning of the operation it is permissible to remove 20 per cent of the total blood volume (1,000 cc. in adults) before any of the donors' blood is given. This amount is gradually replaced during the transfusion. When it is possible, this procedure increases the efficiency of the exsanguination by removing a large volume of the patient's blood before it is mixed with any of the donors' blood.

The blood is exchanged at a rate of 500 cc. every five to ten minutes. When the exsanguination is discontinued, an injection of blood equal to 10 per cent of the blood volume of the body (500 cc. in adults) is given in excess of the amount removed. This compensates for the dilution of the blood injected. Further information was given by Buhot.[17]

16. Dausset, J., and Moulinier, J.: Une technique d'exsanguino-transfusion avec un nouvel appareil, Sang **19**:538, 1948.

17. Buhot, S.: Technique de l'exsaguino-transfusion chez le nouveau-né, l'enfant et l'adulte, Rev. d'hémat. **3**:92, 1948.

REPORT OF CASES

I present here reports of only 3 typical cases. In 2 cases the patient was treated exclusively by replacement transfusion; in the third, the patient was treated by replacement transfusion associated with peritoneal dialysis.

CASE 1.—Mrs. D., a woman of 25 years, had hepatorenal syndrome with Clostridium perfringens sepsis after a nonaseptic criminal abortion. At the onset the temperature reached 104 F. and dark and generalized icterus appeared. The

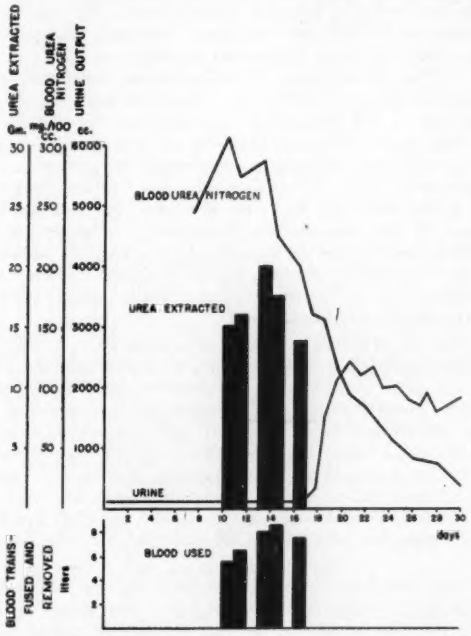

Fig. 2.—Replacement transfusion in Mrs. D. (case 1).

urine became very dark and diminished progressively in quantity until complete anuria was present. The blood urea nitrogen rose, and hemorrhagic diathesis appeared, with epistaxis, menorrhagia and rectal bleeding. At the time of hospitalization the level of blood urea nitrogen was 307 mg. per hundred cubic centimeters; the red blood cell count was 2,100,000 and the white blood cell count 40,000. The patient was in a comatose condition, and the prognosis seemed hopeless.

On the eleventh day of anuria a replacement transfusion of 5,500 cc. was performed (fig. 2). This amount was approximately one and one-fourth times the total blood volume. A total of 15 Gm. of urea nitrogen was recovered from the

expelled blood. After the replacement transfusion the patient was much improved. The hemolytic jaundice and the nervous and hemorrhagic symptoms had diminished. On the next day of anuria a second replacement transfusion was performed. The level of blood urea nitrogen at that time was still high (275 mg.). A total of 6,400 cc. of blood was used in the second transfusion, and 16 Gm. of urea nitrogen was recovered from the exsanguinated blood. Again the patient improved: The blood pressure increased, and the hemorrhagic symptoms vanished almost completely. The level of blood urea nitrogen after this procedure was 237 mg. On the thirteenth day of anuria no transfusion was given and symptoms referable to the central nervous system increased. The third replacement transfusion, using 7,750 cc., was performed on the fourteenth day of anuria. A total of 20 Gm. of urea nitrogen was recovered from the removed blood. The level of blood urea nitrogen dropped to 207 mg., and the icterus completely disappeared. On the fifteenth day of anuria a fourth replacement transfusion of 8,300 cc. of blood was given and 16.10 Gm. of urea nitrogen was recovered. After this procedure the level of blood urea nitrogen was 157 mg. On the sixteenth day 150 cc. of urine appeared; however, a fifth replacement transfusion was done on the seventeenth day, using 7,500 cc. of blood, and 13.80 Gm. of urea nitrogen was recovered. There was a considerable increase in urine output on that day, to a total of 2,000 cc. Subsequent recovery was uneventful, but the blood urea nitrogen did not reach a normal level until the thirty-third day. The total amount of blood transfused was 38 liters, and the total amount of urea nitrogen extracted was 82.5 Gm. Three months later the hippuric acid clearance test showed 93 mg. in twenty-four hours (normal is 500 mg.) and the test for glomerular clearance with mannitol showed 97 cc. per minute (normal is 100 to 150 cc.), indicating some tubular but scarcely any glomerular damage.

Case 2.—Mr. M., 42 years old, ingested by accident 1 Gm. of mercuric chloride (corrosive sublimate). When he was admitted his general condition was still good but oliguria was severe (there was 150 cc. of urine per day). Splanchnic infiltration and intravenous injections of procaine hydrochloride were ineffective.

From the seventh until the sixteenth day eight replacement transfusions were given daily or (at the end of the treatment) every two days. Each replacement transfusion was given with an amount of blood equal to one or one and one-fourth times the total blood volume of the patient. These quantities were 4,000, 3,650, 6,000, 5,000, 5,000, 5,500, 6,000 and 6,000 cc. By this procedure it was possible to remove from the patient's body 5.5, 5, 8, 6.5, 6, 6.5, 8.5 and 6 Gm. of urea nitrogen respectively.

The total amount of blood used was 41 liters, and the total amount of urea nitrogen removed by exsanguination was 51.5 Gm. The amount of urea nitrogen eliminated by the urine during that time was 11 Gm.; the sum of the amounts of urea nitrogen extracted by replacement transfusion and eliminated in the urine was 62.5 Gm. in ten days. The average amount of urea nitrogen eliminated daily by the body was 6.5 Gm., i. e., a little more than the daily ureogenesis. The level of blood urea was stabilized from the beginning of the treatment by replacement transfusion. The resumption of the urine output began on the fifteenth day.

There was evidence of serious renal damage (polyuria and low urea concentration in the urine) three months after recovery from the acute episode.

Case 3.[18]—Mrs. V., a 22 year old woman, was admitted to the hospital with hepatorenal syndrome and Cl. perfringens sepsis after a nonaseptic procedure for

18. Dérot, M.; Tanret, P.; Solignac, H., and Delaveau, P.: Nouveau cas d'hépatonéphrite à "B perfringens" guéri par la dialyse péritonéale et l'exsanguino-transfusion, Bull. et mém. Soc. méd. d. hôp. d. Paris **64**:1227, 1948.

criminal abortion. Total anuria was present. The patient was pale and weak, with minimal conjunctival icterus. She was perfectly clear mentally. No hemorrhagic manifestations were present. The alkali reserve was 22 volumes per cent, and the blood p_H was 7.55. A replacement transfusion (fig. 3) was preformed on the ninth day of anuria, at which time the level of blood urea nitrogen was 200 mg. A total of 7,000 cc. of blood was given and the same amount removed. Twelve grams of urea nitrogen was recovered from the removed blood. On the tenth day of anuria peritoneal irrigation was performed with 15 liters of diluting solution, 18 Gm. of urea nitrogen being removed from the patient; on the eleventh day 6 liters were used, and 9.3 Gm. of urea was removed. The level of blood urea nitrogen dropped to 145 mg. at that time, but the alkali reserve remained low (27 volumes) and the

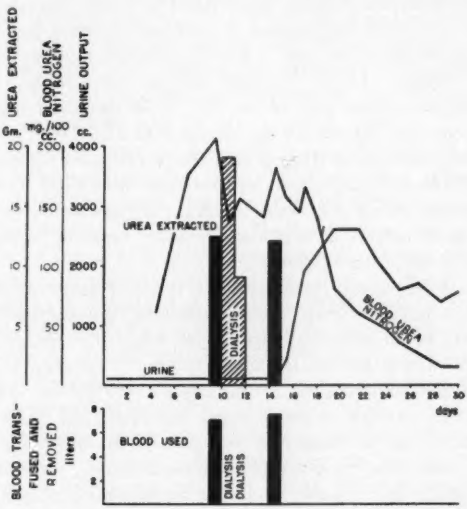

Fig. 3.—Replacement transfusion in Mrs. V. (case 3).

general condition of the patient remained poor. A second replacement transfusion was given on the fourteenth day of anuria, using 7,500 cc. of blood; 11 Gm. of urea nitrogen was recovered. The alkali reserve had increased to 34 volumes. The day after this second replacement transfusion a great volume of urine was excreted, and the patient rapidly recovered. Two months later, however, there was still some evidence of impairment of renal function.

COMMENT

Replacement transfusion in adults confronted us with a new problem. The theoretic question arose whether the transfusion of blood taken from 10 to 20 donors could cause occasional severe or even fatal reactions. It is well known that the newborn infant can survive almost total replace-

ment of its blood volume with blood from a single donor. However, it was feared that in adults the introduction of a mixture of foreign proteins would cause allergic accidents due to antibodies possessed by the recipient, or those transmitted by the blood injected; the possibility of such accidents would be increased in proportion to the number of donors used.

Extensive experience, based on more than 500 operations, has proved that the operation is not only possible but is tolerated well.

Indications.—The best application of this new technic of transfusion is in the treatment of patients with acute intoxication. It is especially useful in the acute intoxication of azotemia in lower nephron nephrosis. Whereas in peacetime the number of patients requiring such treatment is comparatively small, in time of war the frequency of anuria was considerably increased. Lucke [19] pointed out that lower nephron nephrosis was observed in 10 per cent of the first 1,000 autopsies performed in the Mediterranean Theater during World War II. This high incidence is easily understood when it is realized that transfusion incompatibilities, burns, multiple wounds, crush injuries and blackwater fever all can lead to obstruction of the renal tubules. Replacement transfusion is recommended whenever there is lower nephron nephrosis with prolonged anuria due to any of these causes.

Causes of anuria can be classified in two important categories:

The first includes renal failure following the liberation into the blood stream of an abnormal quantity of heme pigments. Not every instance of acute hemolysis leads to renal failure; only extensive hemolysis occurring in a relatively short period will produce lesions of the tubules. Such rapid liberation of large amounts of hemoglobin can be caused by any one of the following accidents: serologic hemolysis (transfusion incompatibility); infections (septicemia with Cl. perfringens); ingestion or inhalation of poisons (halogenated derivatives of hydrocarbons, DDT,[20] arsenic hydride, copper sulfate), or physical causes (extensive burns,[21] heat stroke,[22] march hemoglobinuria [23]). The liberation of myohemoglobin is responsible

19. Lucke, B.: Lower Nephron Nephrosis (Renal Lesions of Crush Syndrome, of Burns, Transfusions, and Other Conditions Affecting Lower Segments of Nephrons), Mil. Surgeon **99**:371, 1946.

20. Smith, N. J.: Death Following Accidental Ingestion of DDT: Experimental Studies, J. A. M. A. **136**:469 (Feb. 14) 1948.

21. Shen, S. C., and Ham, T. H.: Studies on Destruction of Red Blood Cells: Mechanism and Complications of Hemoglobinuria in Patients with Thermal Burns, New England J. Med. **229**:701, 1943.

22. Malamud, N.; Haymaker, W., and Custer, R. P.: Heat Stroke, Mil. Surgeon **99**:397, 1946.

23. Gilligan, D. R., and Blumgart, H. L.: March Hemoglobinuria, Medicine **20**:341, 1941.

for lower nephron nephrosis in the crush syndrome [24] and after similar accidents, in multiple wounds and in wounds and/or thrombosis of large vessels. In patients subjected to extensive surgical therapy and in women with uteroplacental damage a similar mechanism is in operation.[25] The liberation of methemoglobin is responsible for renal accidents in blackwater fever.[26] This process can also have a toxic origin, such as intoxication produced by ingestion of sodium chlorate.[13]

The second category includes intoxication due to poisons with specific action on the epithelium of the renal tubules. The heavy metals, especially mercury, are known to act in this manner. The damage to the renal tubules incident to sulfonamide intoxication can occur as a result of hemolysis. Some cases of anuria which have been observed after intractable vomiting [27] or massive absorption of sodium bicarbonate cannot be included in this classification. Lastly, the acute nephrosis of shock must be mentioned.

Efficiency.—The purpose of replacement transfusion is to remove nonprotein nitrogen from the body. The efficiency of replacement transfusion depends on three factors: It is proportional to the quantity of blood used in regard to the total blood volume of the patient, proportional to the initial level of blood nonprotein nitrogen and inversely proportional to the speed of the operation. The last factor can hardly be considered, as it is impractical to prolong the operation more than two or three hours because of the discomfort to the patient.

In the case of replacement transfusion in the treatment of patients with anuria the percentage of replacement is not so important as is the quantity of blood which passes through the body of the patient in relation to total blood volume (total blood volume is equal to one thirteenth of the body weight). Experience has shown that the best results, at least with the speed usually employed, are obtained with the use of a quantity of blood equal to one-half or two times the total blood volume of the body. Beyond this volume, the efficiency is lessened as the expelled blood fails to remove sufficient additional nitrogenous waste.

Table 1 shows the variations in the number of grams of urea nitrogen extracted from 1 patient, whose weight was 143 pounds (65 Kg.) and whose blood volume was 5 liters. The number of grams of urea

24. Bessis, and Umdenstock, R.: Etude anatomique et considérations thérapeutiques sur le syndrome de Bywaters, Rev. d'hémat. **3**:426, 1948.

25. Paxson, N. F.; Golub, L. J., and Hunter, R. M.: Crush Syndrome in Obstetrics and Gynecology, J. A. M. A. **131**:500 (June 8) 1946. Young, J.: Renal Failure After Utero-Placental Damage, Brit. M. J. **2**:715, 1942.

26. Foy, H.; Altmann, A.; Barnes, H. D., and Kondi, A.: Anuria, with Special Reference to Renal Failure in Blackwater Fever, Incompatible Transfusions and Crush Injuries, Tr. Roy. Soc. Trop. Med. & Hyg. **36**:197, 1943.

27. McLetchie, N. G. B.: Renal Lesions in Case of Excessive Vomiting, J. Path. & Bact. **55**:17, 1943.

nitrogen removed was dependent on the initial level of blood urea nitrogen and on whether replacement was made of one or two times the total blood volume (5 or 10 liters of blood plus anticoagulant). The number of grams extracted was computed according to the concentration of urea nitrogen in the removed blood, averaging initial and terminal samples.

Thus an average of 10 to 20 Gm. of urea nitrogen can be removed from the adult with azotemia by the described method of replacement transfusion. This amount represents the accumulated urea nitrogen of two to three days of ureogenesis.

Experience acquired during the treatment of patients with anuric nephrosis in whom the level of urea nitrogen was particularly high showed that the urea nitrogen passes very quickly from the tissues into the blood stream. Therefore, the decrease of blood urea nitrogen between the taking of the first and last blood sample is relatively small, even with

TABLE 1.—*Urea Nitrogen Extracted from 1 Patient*

Initial Level, Mg./100 Cc.	Amount Extracted by Replacement Transfusion, Gm.	
	1 × Total Blood Volume	2 × Total Blood Volume
250	12	20
200	10	16
150	6.7	12
100	4.5	8

a replacement of 95 to 99 per cent of the patient's total blood volume. When twice the total blood volume is transfused it can be expected that the urea nitrogen will be decreased by one third of its initial value. However, on the day after the replacement transfusion the blood urea nitrogen level would be expected to show a definite increase in a patient with total anuria. Therefore, the total decrease in urea nitrogen is generally not more than 25 per cent of its initial value.

Treatment.—According to what has been stated it is clear that the essential factor in the treatment of an anuric patient by replacement transfusion consists in calculating the quantity of blood needed to balance the ureogenesis, thus keeping the urea nitrogen at a level not immediately dangerous to life. There is evidence that a urea nitrogen level of 125 mg. should be reached before replacement transfusion is indicated. Below this level, the blood urea nitrogen should be observed until renal function is resumed. It is known that daily ureogenesis produces 5 to 8 Gm. of urea nitrogen; therefore, a quantity of urea nitrogen calculated on this base should be extracted when replacement transfusion is used at one, two or three day intervals.

Sometimes the patient is not completely anuric and eliminates a small amount of urea nitrogen in the urine. This amount is in most cases negligible; yet, the principle could be accepted that the sum of the urea nitrogen eliminated eventually in the urine and of the urea nitrogen extracted by replacement transfusion should reach a daily minimum average of 5 to 8 Gm. Using this principle one is able to keep an accurate account of the urea nitrogen balance of the patient, and undue optimism is guarded against when urine production is resumed, for often this urine has an extremely low concentration of urea nitrogen.

In order to achieve this result it is often necessary to carry out a replacement transfusion every two days, using a volume of blood equal to one half or two times the total volume of the patient's blood.

Sometimes the problem is different, for example, when the patient has a level of blood urea nitrogen already beyond the limit of 125 mg. and stupor and other signs of uremia have appeared. Then it is imperative that the level of urea nitrogen be brought back to a lower level. This result may be obtained by the daily repetition of massive replacement transfusion, as in the first case that presented. Evidence has been given of the important decrease in urea nitrogen that can be expected, but daily and massive replacement transfusions represent heroic treatment that can sometimes be avoided by undertaking an early cure.

In other cases, good use can be made of the association of replacement transfusion with peritoneal irrigation (or the use of the artificial kidney). The possibilities of the methods of dialysis and of replacement transfusion are not the same. Replacement transfusion enables one to liberate the organism from nondialyzable heme pigments when these are dissolved in plasma. It is indeed useful to extract these large protein molecules responsible for renal damage, even when renal failure is already present. It is likely that their presence prevents the functional recovery of the kidneys. In fact, the question arises whether replacement transfusion undertaken very early, as an emergency procedure, after a severe hemolytic accident might not prevent or attenuate renal damage. Besides, replacement transfusion tends to normalize the humoral balance and reestablishes a normal number of blood cells. On the other hand, peritoneal dialysis is a simple and economical process, but it has its drawbacks in that it extracts only dialyzable substances and does not restore a humoral balance previously destroyed. The association of both methods proved efficient. The best way of combining them is, in most cases, the following: A replacement transfusion is done soon after the accident, partly to eliminate the heme pigment or the poison responsible for anuria, and peritoneal dialysis is then undertaken for twelve or twenty-four hours. In order to avoid formation of adhesions in the peritoneum, the dialysis is then discontinued. If resump-

tion of the urine output is not obtained and if the poor condition of the patient persists, a second and sometimes a third replacement transfusion should be done. Usually diuresis appears before this time. The same combination of therapy could theoretically be accomplished with the artificial kidney.

The adjuvant treatment with replacement transfusion is simple. Replacement transfusion should always be done with the protection of penicillin (500,000 units per day) in order to lessen the risks of accidental contamination of the blood. The water balance, also, should be strictly watched in these patients. Experience proved that hydration was more dangerous than efficient and that injection of saline or dextrose solution should be resorted to only in case of vomiting or of profuse diarrhea. In all other instances the dilution of the blood injected should be sufficient to balance the losses in water occasioned by sweating.

Physiologic Effects.—Replacement transfusion replaces polluted blood with normal blood which has been circulating in normal donors' kidneys. It forms, therefore, a partial parabiosis between the patient's organism and several healthy organisms. Clinically, the partial reinstatement of humoral balance and the repair of anemia are made obvious by a definite improvement of the patient's condition. When there have been nervous signs there is a decrease of drowsiness and of stupor, and when there have been hemorrhagic signs they become lessened or are stopped. However, in the severest cases these effects are short lived and the replacement transfusion should be repeated to obtain permanent improvement.

It is well known that the specific humoral defect of anuric patients consists of an impressive depletion of alkali reserve, a decrease in chlorides and an increase in potassium and phosphates. The injected blood rapidly takes on the same characteristics, but they are always less acute than before replacement transfusion. The alkali reserve, for instance, shifts on the average from 21 to 36 volumes, but the benefit of the operation is merely temporary. Replacement transfusion is a temporary measure that enables the patient to gain time.

Replacement transfusion has no direct action on the kidney, and the resumption of urine output remains independent of the procedure. In a few cases Tzanck and I [10] observed a peak in the urine output after replacement transfusion, even with an increase of urea concentration, but such cases are exceptional.

Advantages and Disadvantages.—Replacement transfusion has proved to be an efficient method of treatment of patients with acute azotemia, but the method has the disadvantage of requiring large quantities of relatively fresh blood of a compatible type. This disadvantage is lessened by the use of type O blood and of Witebski substances in

patients with blood of type A, B or AB. It is hardly conceivable that a blood bank could not supply 7 liters of blood or provide the required number of donors.

Transfusion reactions are identical to those occurring after ordinary transfusions (chills, urticaria, etc.). The frequency of such reactions is multiplied by a great number of donors. During the two days following the procedure, fever is often observed. Serologic accidents should be avoided by the careful testing of blood types and by agglutination tests. These precautions are particularly required in patients who have already received a sensitizing transfusion and in women after one or several pregnancies. No accident has yet been reported.

TABLE 2.—*Data on 44 Patients Treated by Replacement Transfusion*

Number of Patients	Diagnosis	Replacement Transfusion: Alone	Replacement Transfusion: With Peritoneal Dialysis	Patients Recovered
24	Hemolytic septicemia (Cl. perfringens or hemolytic streptococcus)	17	7	First group, 11; Second group, 6
3	Mercury poisoning	2	1	1 in each group
1	Nephrosis due to sulfonamide	1	0	1
1	Intoxication with sodium chlorate	0	1	1
1	Oliguria following severe burn	1	0	1
1	Transfusion reaction	0	1	1
6	Postoperative anuria	6	0	3
1	Anuria during attack of blackwater fever	1	0	0
3	Hepatonephrosis of undetermined origin	3	0	1
3	Postscarlatinal nephrosis	3	0	3

An objection to this method is seen in the possibility of the transmission of the virus of homologous serum jaundice. This fear is justified by the frequency of this complication in the United States.

These disadvantages are greatly compensated by the utility of the method. This utility is most strikingly demonstrated in three instances: first, when anuria is traceable either to accidental or criminal poisoning or to the passage of heme pigments into the blood stream (presently, only replacement transfusion is able to remove the nondialyzable poisons often linked with proteins and those nondialyzable pigments); secondly, when the poor condition of the patient forbids the use of dialysis, especially when there is hemorrhagic diathesis, and thirdly, when replacement transfusion is used alternatively with dialysis.

In these considerations it is implied that replacement transfusion is not opposed to the dialysis methods but, on the contrary, complements them.

Results.—This method, known in France as Bessis' method, was employed there in 44 cases; twenty-nine recoveries were obtained. Data were as indicated in table 2.

The number of replacement transfusions needed to obtain recovery is extremely variable, according to the cases. It may be from one (usually when peritoneal dialysis is associated) to eight, with an average of three to four. The quantity of blood used per transfusion has been equal on the average to one and a half times the total blood volume of the patient. The duration of the anuria has also been variable (between ten and eighteen days), but it is significant that the average duration of the anuria was sixteen days (in 4 cases the anuria lasted seventeen days, and in 1 case, twenty-three days). This duration is identical whether replacement transfusion is employed alone or with dialysis.

This duration shows that most such patients could not have recovered spontaneously.

Failures were due mostly to unjustified delay of the replacement transfusion or to the trial of surgical methods of treatment. In all cases in which the treatment was followed as described for as long as the situation required, success was achieved.

The renal tests of patients after "recovery" showed that this was not total, as it is generally believed to be, and that a deficit involving exclusively the tubules remained. The clearance of tubules, tested with paraaminobenzoic acid, often shows a half deficit two or three months after the accident. The sequelae are definitively worse after lower nephron nephrosis due to poisoning with heavy metals than after nephrosis due to precipitation of heme pigments.

Conclusion.—Repeated replacement transfusion is a theoretically ideal treatment for acute total renal failure. If replacement transfusion could be done almost continuously, the renal function would be wholly substituted. However, replacement transfusion in adults is an expensive procedure and its use must be exclusively limited to patients in the acute phase of lower nephron nephrosis. Replacement transfusion permits the patient to survive for the few days needed for the functional recovery of the kidneys.

SUMMARY

Patients with the anuric phase of lower nephrone nephrosis can be efficiently treated by repeated replacement transfusion.

1. The technic of replacement transfusion in adults is briefly described.

2. Replacement transfusion is useful whatever the origin of the lower nephron nephrosis but more particularly in failures due to the presence in the blood stream of a nondialyzable heme pigment (as in transfusion incompatibilities, massive hemolysis, crush syndrome or burns) or of a poison linked with a nondialyzable protein. Experience has proved the efficiency of this method in the most severe cases with nervous and hemorrhagic signs (Cl. perfringens sepsis).

3. The study of the decrease in the level of blood urea nitrogen after replacement transfusion shows that the replacement with a quantity of blood equal to the total blood volume of the patient's body merely enables one to maintain the urea balance, and that the replacement by a quantity equal to two times the blood volume of the patient enables one to lower the blood urea nitrogen by 33 per cent from beginning to end of the procedure and by 25 per cent the day after the procedure. The importance and frequency of the replacement transfusions should be calculated accordingly.

4. Physiologically, replacement transfusion enables one to remove from the organism urea and all abnormal substances, whether they are proteinic or crystalloid and whether they are dialyzable or not. Replacement transfusion is particularly efficient in removing the heme pigments often responsible for renal failure and the proteins linked with poisons. Replacement transfusion improves the humoral balance and repairs the anemia, therefore improving the general condition strikingly. Alternative use of methods of replacement transfusion and dialysis is in many cases a good solution.

5. Using this method in France 29 recoveries in 44 cases were obtained.

HYPERTENSIVE CARDIOVASCULAR DISEASE (ACUTE) (MALIGNANT HYPERTENSION)

Clinical and Pathologic Study of Thirty-Nine Cases

JOHN E. KOEPSELL, M.D.
JOSEPH F. KUZMA, M.D.
AND
FRANCIS D. MURPHY, M.D.
MILWAUKEE

THERE is no unanimity of opinion regarding the proper place in the classification of hypertensive cardiovascular disease of the acute form, often called malignant hypertension, and there are even some writers who have stated that the term should be dropped entirely. The confusion regarding nomenclature in the study of this condition has led some to believe that malignant hypertension is a disease *sui generis,* unrelated to other forms of hypertensive cardiovascular disease. From the observations of one of us (F. D. M.) and an associate, published previously,[1] it was our opinion at that time that malignant hypertension did not differ in kind from benign hypertensive cardiovascular disease but that the difference was merely one of degree. In this study we changed our mind regarding the course, the prognosis and the treatment of malignant hypertension.

For the purpose of this paper, 39 cases of malignant hypertension were studied clinically and at autopsy. Sixteen of the cases reported in 1930[1] were reviewed, and 23 new cases were added. In this entire series, 38 of the patients died and autopsy was performed on 33 of them. It is our desire to present a clearer clinical and pathologic picture of malignant hypertension and to emphasize the importance of its early recognition and prompt treatment. This study does not include all the cases of malignant hypertension observed by us, but only those which were studied completely, being seen in the early stages and observed clinically to death or as in case 3, to apparent remission at the time of writing.

Attention in this series was given to the 23 cases studied since 1930, and the clinical and pathologic features are presented. A general discus-

From the Departments of Medicine and Pathology, Marquette University School of Medicine and Milwaukee County Hospital.

1. Murphy, F. D., and Grill, J.: So-Called Malignant Hypertension: A Clinical and Morphological Study, Arch. Int. Med. **46**:75-104 (July) 1930.

sion of the pathologic findings is also given. Special emphasis is placed on those cases showing certain exceptions in the clinical course, such as spontaneous remission, absence of the classical eyeground changes of malignant hypertension and development of the cardinal changes before the onset of albuminuria and other evidences of renal disease.

ANALYSIS OF THE CLINICAL DATA

The clinical manifestations seen in this series of cases varied considerably as heart failure, renal failure or cerebral accidents developed or as the rate of progress of the disease changed.

In the 39 cases reviewed, the age of the patients ranged from 9 to 78 years. The majority of patients were between the ages of 33 and 55. Twenty-seven patients were over 40, and 12 were under 40. Sixteen were over 50, whereas 3 were under 19. This confirms the findings of Keith, Wagener and Kernohan,[2] whose series of patients ranged in age from 9 to 64 years, the average being 42. In a study made by Klemperer and Otani [3] the average age was 39 years, and these authors quoted Fahr as saying that the age of onset in female patients is around 44, whereas in males it is 30.

Volhard and Fahr [4] found a sex ratio of 30 male to 9 female patients in a study of 39 cases. In our series the sex and race of the patients appeared to have no influence on the severity of symptoms or the rapid progress of the disease.

It was difficult to be certain whether all patients had a benign form of the disease before the onset of malignant hypertension, as many patients had the malignant phase on first examination. However, when it was possible to determine its presence, benign hypertensive cardiovascular disease preceded the acute, or malignant, phase for several months to ten years. Of the 33 patients on whom autopsy was performed, in 8 the disease was present for less than five years, in 13 it was present for more than five years and in the remaining 12 it was of undetermined duration. In several cases there was no previous knowledge of the disease. No history of preexisting renal disease was obtained in any of these cases. One of the patients had chronic lead poisoning, a condition which Derow and Altschole [5] found in association with malig-

2. Keith, N. M.; Wagener, H. P., and Kernohan, J. W.: The Syndrome of Malignant Hypertension, Arch. Int. Med. **41**:141-188 (Feb.) 1928.

3. Klemperer, P., and Otani, S.: Malignant Nephrosclerosis, Arch. Path. **11**:60-117 (Jan.) 1931.

4. Volhard F., and Fahr, T.: Die Brightsche Nierenkrankheit: Klinik, Pathologie und Atlas, Berlin, Julius Springer, 1914.

5. Derow, H. A., and Altschole, M. D.: Nature of Malignant Hypertension, Ann. Int. Med. **14**:1768-1780 (April) 1941.

nant hypertension in some cases. Chronic nephritis and acute nephritis were not present in this series, although the condition of 2 patients was diagnosed clinically as chronic nephritis, which was not borne out at autopsy. No eclampsia or other form of renal disease was found.

Malignant hypertension is a syndrome involving many organs and systems of the body; consequently, there was widespread variation of the clinical features. Headache was the commonest and earliest symptom that appeared, being present in 85 per cent of the 39 patients. Other common symptoms were dyspnea, dizziness and visual disturbances, in the percentages listed in table 1.

The significant physical findings involved the blood pressure or the eyegrounds, the heart or the kidneys. In the series of 33 patients examined at autopsy, the diastolic pressure ranged from 100 to 190, with an average of 145, whereas the systolic pressure ranged from 200 to 300,

TABLE 1.—*Frequency of Symptoms in Patients with Malignant Hypertension*

Symptom	Percentage
Headache	85
Dyspnea	54
Dizziness	40
Visual disturbances	40
Loss of weight	33
Weakness	29
Nausea and vomiting	27
Precordial pain	18
Paralysis	12
Abdominal pain	9
Hematuria (gross)	9
Syncope	6
Epistaxis	3

the average being 235. The degree of anemia was not striking in the early phases of the disease. The red blood cell count averaged 3,100,000 terminally.

In all patients except 4 the classical findings of papilledema, hemorrhages, exudation and sclerosis of the retinal vessels were present in varying degrees. In the remaining 4 patients papilledema was absent, but there were varying degrees of retinal sclerosis, hemorrhages and exudation. The following case was characteristic of this group.

CASE 1.—C. S., a 35 year old Negro man, entered the hospital with a history of sudden onset of diplopia one month prior to admission. Intermittent dull supraorbital and occipital headaches, marked anorexia and a weight loss of 10 pounds (4.5 Kg.) subsequently developed. No other symptoms were noted.

The past history was noncontributory. The patient had never been aware of hypertension prior to the present illness.

Physical Examination.—This revealed a well developed, well nourished Negro man in no acute distress. The blood pressure was 230 systolic and 150 diastolic. The fundi showed flat disks, dilated, tortuous veins, greatly narrowed arteries, arteriovenous nicking and numerous white patches. No hemorrhages were seen. The lungs were clear to auscultation and percussion. The heart was not enlarged;

the aortic second sound was tambour in type, and a soft apical systolic murmur was present. The abdomen, extremities and neuromuscular system were normal. The rectal examination was noncontributory.

Laboratory Examination.—The red blood cell count was 2,450,000. Urinalysis showed a specific gravity of 1.010, with albumin (2 plus) and a few casts. The Addis count revealed 8,200,000 red cells and 4,300,000 white cells in the twelve hour specimen. The nonprotein nitrogen level on admission was 66.2 mg. per hundred cubic centimeters and rose steadily to a maximum of 333 mg. The urea nitrogen level rose to 257.5 mg. per hundred cubic centimeters. The alkali reserve was 54.3 volumes per cent on admission and fell to 26.9, and the serum sodium level of 140 milliequivalents fell to 134. The serum potassium level was 2.0 milliequivalents and rose to 8.5.

The intravenous pyelograms were normal. A roentgenogram of the chest on admission was normal; later roentgenograms showed cardiac enlargement. Serial roentgenograms of the gastrointestinal tract were normal. The electrocardiogram on admission revealed changes which were compatible with hypertrophy of the left ventricle. An electrocardiogram taken on the forty-sixth day indicated an intraventricular conduction defect.

Course.—The patient was placed on a weighed low sodium diet. The intake of sodium varied from 177 to 400 mg. a day. He also received rutin, ascorbic acid and phenobarbital. The headaches and diplopia persisted. Progressive uremia developed, manifested by a rising nonprotein nitrogen level, epigastric pain, nausea, vomiting and diarrhea. On the thirty-sixth hospital day the low sodium diet was discontinued and the patient was given sodium chloride solution intravenously because of associated hyperkaliemia with heart block. On the forty-fourth hospital day the patient went into cardiac failure and was digitalized. On the forty-sixth day urea frost developed, and he died on the following day.

In spite of repeated funduscopic examinations, at no time was papilledema noted.

Postmortem Findings.—Numerous subcapsular hemorrhages were present about both kidneys. An infarct was present in the right kidney. The capsule stripped with difficulty. The cut surface through the kidneys revealed congestion of the medulla and numerous reddish blue areas of discoloration throughout the cortex. On microscopic examination of the kidneys, the glomeruli were found to be swollen and the tubules exhibited degenerative changes. Numerous foci of lymphocytes were present. The vessels were extremely congested. The small blood vessels were greatly thickened, and some arteriolar necrosis was present. The glomeruli contained large amounts of pink-staining material separating the cellular elements. Some elements were completely hyalinized. The heart weighed 500 Gm. and was surrounded with shaggy, fibrinous exudate. The coronary vessels were thickened, and a moderate amount of fibrosis was present. The spleen was greatly congested. The small vessels of the spleen were greatly thickened. Petechial hemorrhages were found in the duodenum and ileum. There were hyperplasia and congestion of the adrenal glands and hydropic degeneration and focal necrosis of the liver.

In the series studied since 1930, it was found that the heart was enlarged in all patients. The size of the heart varied from 350 Gm. to 675 Gm., averaging 473 Gm. in the 22 patients on whom autopsy was performed. Although the heart was enlarged in all patients, the enlarge-

ment in the majority was moderate. MacMahon and Pratt [6] found in their study of 60 patients that the average weight of the heart was around 600 Gm. and that the left ventricle showed marked concentric hypertrophy. Derow and Altschole [5] found that in their 15 patients the heart varied from 250 to 830 Gm., the average weight being 550 Gm. Shapiro [7] did not give the weight of the heart in grams, but he did mention that the hearts in his series were all very large, far exceeding the normal weight.

Of the 22 patients examined at autopsy since 1930, cardiac murmurs had been present in 9. An apical systolic murmur had been present in all the 9 patients, and in 2 patients a systolic murmur over the aortic area had also been present. Fourteen of the 22 patients had heart failure. In those patients for whom electrocardiograms were made, the changes were usually those of hypertrophy of the left ventricle. The T waves were usually low or inverted, with depression of the S-T segments. Markham and Bloom [8] indicated that these changes show the presence of myocardial damage and are only coincidentally related to the cardiac size. These changes also indicate a serious prognosis for the immediate future of the patient. Atrial fibrillation was present in only 2 of our patients, but gallop rhythm was commonly found; other irregularities were not noted.

Renal function was normal or only slightly impaired in the majority of patients. Pronounced impairment of renal function was present in about one third of the patients (tables 2, 3 and 4).

In 1 patient the cardinal changes of malignant hypertension developed before the onset of albuminuria and other evidences of renal disease.

CASE 2.—*First Admission.*—H. B., a 49 year old white man, was first admitted to the hospital in July 1931, with a cerebrovascular accident. A diagnosis of malignant hypertension was made at that time, based on the blood pressure of 190 systolic and 150 diastolic and on the presence of cardiac hypertrophy and typical eyeground findings of bilateral papilledema, retinal edema, hemorrhages and tortuous and greatly narrowed arterioles. The urine was free of albumin, red blood cells and casts. The specific gravity was 1.010. The hemoglobin concentration was 80 per cent, and there were 4,700,000 red blood cells. Blood chemistry values were as follows: nonprotein nitrogen, 57.6 mg.; urea nitrogen, 35.0 mg.; creatinine, 1.6 mg.; sodium chloride, 320 mg.; cholesterol, 149.7 mg., and total protein, 5.47 Gm. (albumin, 3.67 Gm., and globulin, 1.81 Gm.), per hundred cubic centimeters.

6. MacMahon, H. E., and Pratt, J. H.: Malignant Nephrosclerosis (Malignant Hypertension), Am. J. M. Sc. **18**:221-235 (Feb.) 1935.

7. Shapiro, P. F.: Malignant Nephrosis: Pathogenesis, Arch. Int. Med. **48**:199-233 (Aug.) 1931.

8. Markham, J. D., and Bloom, N.: The Significance of Electrocardiographic Changes in Malignant Hypertension, J. Lab. & Clin. Med. **27**:1156-1163 (June) 1942.

Second Admission.—The patient reentered the hospital on December 12, with complaints of headache, dizziness, weakness, visual disturbances and tinnitus. The blood pressure was 190 systolic and 170 diastolic. Bilateral papilledema with retinal hemorrhages was present. Blood chemistry values were as follows: nonprotein nitrogen, 50.0 mg.; urea nitrogen, 29.4 mg.; sodium chloride, 504 mg.; creatinine, 1.3 mg.; cholesterol, 223 mg., and total protein, 7.31 Gm. (albumin, 3.99 Gm., and globulin, 3.32 Gm.), per hundred cubic centimeters.

Third Admission.—On March 14, 1932, the patient reentered with similar complaints. The blood pressure was 224 systolic and 140 diastolic. The retinal changes were essentially unchanged. The urine remained free of alubmin, casts

TABLE 2.—*Renal Function in Patients with Malignant Hypertension*

	Normal	Impaired		
		Slightly	Moderately	Severely
Phenolsulfonphthalein excretion	22*	22	17	39
Concentration power	14	32	36	18
Urea clearance	20	30	25	25

* All values are percentages of total patients.

TABLE 3.—*Abnormal Elements in Urine of Patients with Malignant Hypertension*

	None	Trace	Moderate Amount	Large Amount
Albumin	4*	27	36	33

* All values are percentages of total patients.

TABLE 4.—*Abnormal Elements in Urine of Patients with Malignant Hypertension*

	None	Few	Many
Red blood cells	41*	34	25
White blood cells	45	52	3
Casts	52	33	15

* All values are percentages of total patients.

and cells. The specific gravity was 1.010. Blood chemistry values were as follows: nonprotein nitrogen, 39.2 mg.; urea nitrogen, 14.0 mg.; creatinine, 2.1 mg.; sodium chloride, 482 mg.; cholesterol, 245 mg., and total protein, 5.45 Gm. (albumin, 3.62 Gm., and globulin, 1.83 Gm.), per hundred cubic centimeters.

Fourth Admission.—The patient's final admission was in August 1933, with complaints of dyspnea, headache, dizziness, vomiting and blurring of vision. The blood pressure was 200 systolic and 144 diastolic. Bilateral papilledema was present, with retinal hemorrhages. Moderate pulmonary edema was present. The heart was enlarged, and the rate was rapid but regular. No peripheral edema was present. The hemoglobin concentration was 70 per cent; there were 3,590,000 red blood cells. The specific gravity of the urine was 1.008; albumin (4 plus) was present, with few granular casts or white blood cells. Blood chemistry values were as follows: nonprotein nitrogen, 60 mg.; urea nitrogen, 37.8 mg.; creati-

nine, 2.5 mg.; cholesterol, 204 mg., and total protein, 6.86 Gm. (albumin, 4.34 Gm., and globulin, 2.52 Gm.), per hundred cubic centimeters. The alkali reserve was 41.2 volumes per cent. Cheyne-Stokes respiration developed, and the heart failure was progressive. Terminal bronchopneumonia developed, and the patient died.

Postmortem Examination.—This revealed advanced generalized arteriosclerosis with pronounced coronary sclerosis and scarring of the heart muscle. Eccentric hypertrophy of the right and left ventricles of the heart was present. Confluent bronchopneumonia of the right lung was noted. The kidneys weighed 140 and 130 Gm., respectively. The capsules stripped with comparative ease. The external surfaces were finely granular. The structure of the parenchyma was indistinct. The renal tissue was indistinct and of a brownish red color, containing irregular-shaped dots and streaks of grayish tissue. The renal pelvis showed isolated small hemorrhages.

Microscopic examination of the kidney showed that the glomeruli were unequal in size. Some were very large and showed some congestion of the capillary loops. In many glomeruli was found a hyaline thickening of some of the capillaries. The vessels in the interstitial tissue were congested, and there were foci of accumulations

TABLE 5.—*Duration of Illness in Patients with Malignant Hypertension*

Duration	Number	Percentage
Less than 6 months	8	24
6 months to 1 year	11	33
1 year to 1½ years	5	15
1½ years to 2 years	4	12
3 years	1	3
4 years	1	3
5 years	1	3
6 years	1	3
9 years or more	1	3
Totals	33	99

of lymphocytic cells within the interstitium. There was extreme sclerosis of most of the arteries, and the arterioles showed extensively thickened walls, very narrow lumens and many segments with arteriolonecrosis.

The muscle fibers of the heart were thickened and hypertrophic and contained large, dark-staining nuclei. The cross striation of the muscle fibers was fairly well preserved. There was proliferation of connective tissue between the fibers. The very small arteries in the myocardium occasionally showed some thickening of the walls.

The duration of illness of malignant hypertension in most patients was from a few months to a year and a half. Table 5 is a breakdown of the patients studied into groups.

One of the most unusual characteristics of malignant hypertension is that occasionally a patient with all the features of the disease will suddenly, without known cause, pass into a stage of almost complete remission, during which the blood pressure falls practically to normal and the signs and symptoms disappear. This remission may last from a few months to many years. Several such cases have been personally observed; the remission occurred independent of any treatment. In such cases as

these, one has always to be on guard for the *post hoc, ergo propter hoc* error in therapeutics. The following case is a representative one of this type.

CASE 3.—This patient, a 46 year old white physician, was first seen in June 1934. The blood pressure was 230 systolic and 160 diastolic. The chief complaints were weakness, headache and palpitation of the heart. There was no edema or azotemia. Urinalysis revealed albumin (1 plus). The microscopic examination of the urine was noncontributory. The patient had very little treatment (mostly the administration of sedatives) but carried on an active general practice. During the next four years he was seen from time to time, and although the urinary findings became more pronounced and the blood pressure remained rather high (240 systolic and 140 diastolic), he continued an active practice. The examination of the eyegrounds showed narrowing of the arteries, fulness of the veins and no hemorrhages, but grade 1 to 2 edema of the optic disks.

In 1937 a profuse pulmonary hemorrhage developed which was thoroughly investigated, but no cause other than hypertension and arteriosclerosis could be found. In 1938 the blood pressure was 260 systolic and 160 diastolic, edema of the ankles developed, and weakness, headache and disturbances of vision became pronounced. Examination of the eyegrounds at that time showed changes typical of malignant hypertension. The patient was seen at a prominent clinic, and the diagnosis of malignant hypertension was confirmed. He then retired from the practice of medicine.

In 1942 he was seen by Dr. Irvine Page, who again confirmed the diagnosis of malignant hypertension. He was treated in the usual way, and in November 1944 the disorders cleared up. The blood pressure dropped to 180 systolic and 120 diastolic. He was examined several times a year. The urine continued to show some albumin, but there was no azotemia and no edema. The edema of the optic disks began to recede. In August 1948 the blood pressure was 170 systolic and 100 diastolic. The patient felt fine but did not return to work.

He was seen in January 1949, and although the blood pressure had not changed an episode of failure of the left ventricle did develop. He was treated for this and made an uneventful recovery.

He was most recently examined in June 1949. The blood pressure was 160 systolic and 90 diastolic, and he felt well and appeared to be progressing satisfactorily.

Note.—Since this article was submitted for publication the patient has died and an autopsy confirmed the diagnosis of malignant nephrosclerosis. The immediate cause of death was cerebral hemorrhage; the contributing cause of death was uremia due to malignant nephrosclerosis.

In this series, the chief cause of death of the 33 patients on whom autopsy was performed was as indicated in table 6.

ANALYSIS OF THE PATHOLOGIC DATA

The kidneys of persons with malignant hypertension are generally well preserved in size. This is significant in the differentiation of malignant hypertension from chronic glomerulonephritis or nephrosclerosis.

The largest kidney of each pair in this series weighed more than 150 Gm. in 70 per cent of the patients; the smaller kidney weighed more

than 120 Gm. in 60 per cent. In general, therefore, the kidney mass in the majority of the instances is well preserved. The capsules were moderately adherent, and in the instances of most acute development the capsules were not firmly attached. In the patients with long-standing antecedent hypertension the kidneys were smaller and the renal capsules more firmly attached. The granularity of the cortical surface is related to the size of the kidneys as well as to the duration of the hypertensive state. In all instances the renal tissue was rather firm and presented an unusually level cut surface and sharp margins. The surface as well as the cut sections was deeply mottled and of a reddish color, with indistinct markings of the parenchyma. In the majority of instances petechial hemorrhages were visible, both on the external surface and on cut sections. Some of these were linear in outline, whereas many were punctate. Hemorrhages in the pyramids were diffuse in character rather than punctate. In 1 instance the hemorrhagic reaction of the kidney was so severe as to resemble a total hemorrhagic infarction of each kidney. The cortex-parenchyma ratio was well maintained in this series. There was

TABLE 6.—*Chief Cause of Death of Patients with Malignant Hypertension*

Cause	Number	Percentage
Uremia	10	30
Heart failure	8	24
Heart failure and uremia	10	30
Cerebrovascular accident	3	9
Bronchopneumonia	2	6
Totals	33	99

no correlation between the position or the anatomic character of the pelvis and the calices. The hilar fat tissue was increased in the instances of very small kidney mass. The larger renal vessels were generally stiff and thick and showed the presence of gross atheromatous plaques.

The histologic changes in the kidneys of persons with malignant hypertension had only one constant identifying feature, namely, the necrotizing change of the preglomerular arterioles, segments of the glomeruli and larger vessels. The large vessels, however, showed considerable elastic hypertrophy and diminution in caliber. Necrotizing changes are frequently seen in the vessels of skeletal muscles, the adrenal capsule, the pancreas and the liver. The necrotizing changes in this series were characterized by the almost complete obliteration of the lumen, loss of intimal surface and the presence of a finely stippled, highly eosinophilic homogenization of the wall substances. This may be uniform in the circumference of the vessel, or it may be present only in part. In some instances there was a continuation of red cell mass from the lumen into the substance of the vessel wall. In many sections lobules or segments of the glomerulus underwent homogenization and acquired a

highly eosinophilic staining character. Such necrosis of the tufts may be continuous with the change in the preglomerular arterioles. The necrosis of the tufts was accompanied with a reaction of surface epithelial cells, with the formation of synechias and inconstant and irregular crescents. The necrosis may be associated with a reaction of polymorphonuclear leukocytes about the periphery and with the extravasation of red blood cells into Bowman's space. The proportion of glomeruli involved was rather inconstant. In the cases in which there was an antecedent history of benign hyperplastic cardiovascular disease, the changes in the vessels were those of severe hyperplastic sclerosis, with tinctorial changes that merged into the arteriolonecrotic features. The identification of arteriolonecrotic changes in terminal benign hyperplastic cardiovascular disease and in uremia is identical to that observed in the clinical case of malignant hypertension, and in some instances the differential diagnosis between the benign form and malignant hypertension may not readily be made on histologic grounds alone. The histologic diagnosis of malignant hypertension developing in the course of benign hypertensive cardiovascular disease and in that of chronic glomerulonephritis may, therefore, be a foremost challenge. In either case the diagnosis is most satisfactorily made on the interpretation of qualitative glomerular changes and quantitative arteriolar changes. Although the glomeruli of hypertensive cardiovascular disease show thickening of the basement membrane, atrophy and hyalinization, accentuated tufts (digitations) are more characteristic than are agglutination of tufts and the presence of synechias and crescents. It is primarily the interpretation of sequelae of inflammation on which the diagnosis of chronic glomerulonephritis may be made. Likewise, the tubular changes in nephritis are severer than those in the benign form of this disease, since there is considerable tubular atrophy and cystic dilatation and many foci of tubular regeneration are present. The arteriolar changes are more prominent in the hypertensive case than in terminal glomerulonephritis. The glomerular arterioles are prominently involved in malignant hypertension, and the glomerular changes accompanying this acute necrotic phenomenon are usually limited to a segment of the glomerulus and are of a thrombonecrotic pattern rather than exhibiting the exudative inflammatory generalized reaction of glomerulonephritis. The vessels in other tissues also show arteriolonecrotic changes more consistent and prominent than those developed in glomerulonephritis. The smallest kidneys in the hypertensive group of patients averaged heavier than the largest in the group with chronic glomerulonephritis. Since the development of uremia takes place over a longer period of time in chronic glomerulonephritis, the features of severe anasarca and hypochromic anemia are more prominent.

The largest number of patients was in the 40 to 50 year age group. In this group the majority of patients had hearts weighing between 400

and 500 Gm., as did one third of the total patients. In approximately one fourth of the patients the hearts ranged between 500 and 600 Gm., the weight not being correlated with age or with the total weight of the kidney. The gross features of concentric hypertrophy were present in the majority of instances, and a thick, shaggy, fibrinous pericarditic deposit associated with uremia was found in approximately one third. Another gross finding consisted of pinhead-sized to pea-sized light yellow-tan areas visible on the epicardial surface or just beneath the epicardium. From the external surface these appeared to be slightly depressed. Such findings were prominent on the lateral and posterior aspects of the left ventricle. This type of necrosis, pointed out by Goulay in 1940,[9] occurred principally in the group with hearts weighing 400 to 500 Gm. In all patients the myocardial mass was firm in consistency, and in those with associated coronary sclerosis small but variable scars were located in the wall of the ventricle. Hypertrophy of the right ventricle occurred, particularly in conjunction with massive hypertrophy of the left ventricle. Of the 22 patients on whom autopsy was performed since 1930, evidence of considerable coronary sclerosis with narrowing of the lumen was present in all but 5. There was evidence of recent myocardial infarction in 1 patient and of an old healed myocardial infarction in 2. This does not bear out the findings of Harrison and Wood,[10] who found that the size of the coronary arteries varied directly with the weight of the heart, whether normal or hypertrophied. They further stated that the coronary arteries of the patients with hypertension were large, with smooth bores.

The histologic changes in the myocardium tend to be related to the duration of the process and to the general state of preservation of the body. Brown degeneration was moderate in the 400 to 500 Gm. group and appeared to be more prominent in the older persons. Scarring of connective tissue was related in a great measure to the state of the coronary vessels. In the patients with acute onset and in those with associated uremia, interstitial edema was prominent. Foci of necrosis, characterized either by intense eosinophilic color or by complete dissolution of the fibers, occurred on the external aspects of the myocardium. Such areas generally were devoid of much cellular reaction.

In this series of cases, the weight of the liver varied considerably and appeared to be more closely related to the age and the general nutritional status of the patient than to the cardiovascular-renal disorder.

9. Goulay, B. A.: The Myocardial Degeneration Associated with Uremia in Advanced Hypertensive Disease and Chronic Glomerular Nephritis, Am. J. M. Sc. **200**:39-49 (July) 1940.

10. Harrison, C. V., and Wood, P.: Hypertensive and Ischemic Heart Disease: A Comparative Clinical and Pathological Study, Brit. Heart J. **11**:205-229 (July) 1949.

The lowest weights were found in the oldest patients, whereas the larger livers generally were found in the somewhat younger group of persons and in those who had short clinical histories and were well preserved. The consistency was increased and the color was usually deep reddish brown. In some instances, either those of very acute onset or those of long-standing heart failure, pinhead-sized areas of necrosis were observed. The histologic changes in the liver sections presented variable degrees of periportal fibrosis with lymphocytic infiltration that were interpreted as independent of any cardiovascular-renal disease, since these are prominent changes with advancing years. However, in many instances the arterioles of the portal areas, although not constantly involved, presented the features of malignant hypertension. The features of arteriolar necrosis are similar to those in the kidney. The dilatation of the sinuses and the atrophy of the central liver cells are related to chronic passive congestion.

In half of the patients the spleen weighed more than the generally accepted normal weight of 150 Gm. The highest weight was 375 Gm. Usually the spleen presented a firm substance with level cut surfaces and small indistinct follicles; fairly prominent trabeculae were noted in the spleens of small size. Histologic examination revealed atrophy of the lymphoid follicles, severe congestion of the red pulp, fibroadenia and severe changes in the arterioles and small arteries. In general most of the central arterioles were severely hyalinized, and in the majority of the patients arteriolonecrosis was not at all difficult to identify.

The pancreas revealed no relation in size to the cardiovascular-renal state. Generally the pancreatic substance was well lobulated, deep tan in color and firm in consistency. The histologic sections showed the significant features of readily identifiable arteriolar changes, which, however, had to be sought with more effort than in the liver.

The adrenal glands varied considerably in size and in gross features. There appeared to be no constant correlation, and the presence of cortical hyperplasia or cortical adenomas was not variable. However, nodules of cortical tissue located centrally in the gland in the medullary substance were conspicuously common in the patients with hypertension. The vessels of the adrenal capsule were almost uniformly involved in the arteriolar changes which make identification of the disease easy from the study of the adrenal capsule.

In the lungs there were no constant findings in the blood vessels related to the cardiovascular-renal state. This is also noted in instances of benign hypertension; however, severe changes in pulmonary vessels occur in pulmonary hypertensive cardiovascular disease but appear to be absent in systemic malignant hypertension.

Separate from the changes of apoplexy and thrombosis there is the frequent change of severe cerebral edema, which if continued may take

the form of multiple microscopic foci of demyelination. These changes are particularly prominent about vessels but occur about neurons and in the brain substance in general. Such perivascular edema associated with a decrease in cerebral circulation apparently accounts for "hypertensive encephalopathy." Pituitary changes were inconstant in this series.

NATURAL HISTORY AND COURSE

Observations on the course of patients with malignant hypertension have required us to modify some ideas expressed previously.[1] It was formerly the general belief that the clinical picture and course of malignant hypertension were rather uniform; however, subsequent observations reported here indicate that there may be a great lack of uniformity in the clinical course.

When the fully developed clinical picture of malignant hypertension is present, the recognition is comparatively easy. In many cases the transition from the benign to the malignant form is abrupt. This period of conversion may occupy a few weeks to a few months, and the classical changes, such as pallor, weakness, anorexia, the alteration in the eyegrounds, headache, an increase of albumin in the urine, hematuria and, finally, uremia, are characteristic. However, this is not always the case. The period of conversion may be slow, occupying a period of years before the fully developed malignant phase is finally reached. In this slow transitional stage the diagnosis may be uncertain.

It is most important, of course, to recognize that the benign form of hypertensive vascular disease has become progressive in nature so that all therapeutic means at hand, including most radical surgical methods, may be used in an effort to stop the trend of the disorder. The indications that the conversion from the benign to the malignant form has begun are as follows:

1. An increase in the blood pressure to a much higher level than that formerly observed. This is particularly true of the diastolic pressure, which rises to 150 or above and persists at this high level.

2. The onset of symptoms such as weakness, anorexia, loss of weight and strength, headaches and a general deterioration of health.

3. Changes in the eyegrounds, such as edema of the disks, hemorrhages and white patches of a special kind.

4. An increase in the albumin, blood and casts in the urine.

It is rather well known that papilledema may be absent, as it was in 16 and 23 per cent of the cases reported by Goldring and Chasis.[11] In

11. Goldring, W., and Chasis, H.: Hypertension and Hypertensive Diseases, New York, Commonwealth Fund, 1944, p. 19.

our series 4 patients, of whom C. S. (case 1) was representative, had all the characteristics of malignant hypertension and died of it without ever having had papilledema.

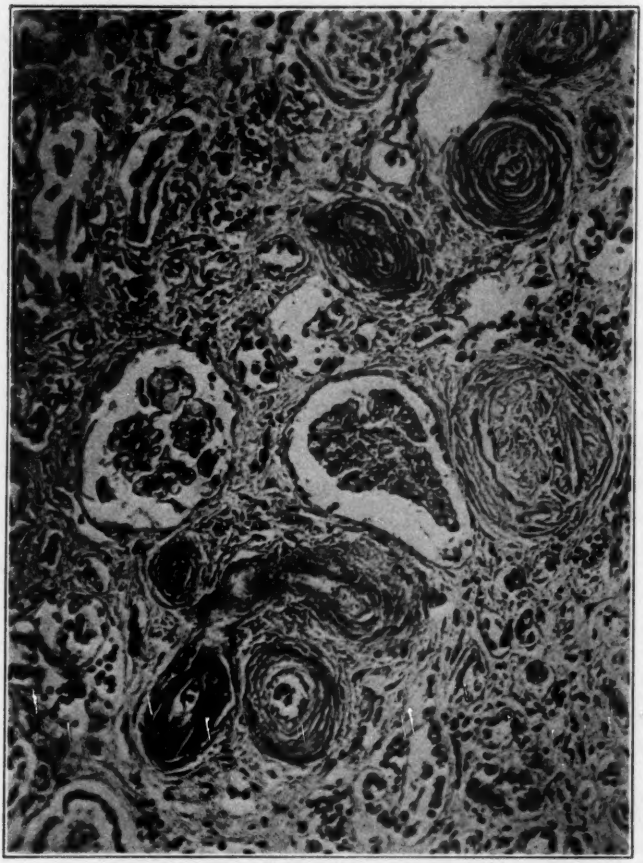

Fig. 1.—Low power magnification of the areas surrounding two glomeruli, showing hyperplastic changes in the small arteries as well as the homogenization necrosis of the preglomerular arteriole. The variation in tubular distribution and the stromal fibrosis indicate antecedent benign hypertensive cardiovascular disease.

It is less well known, however, that malignant hypertension may develop and run a greater part of the course without albuminuria,

hematuria, the presence of casts or the other well known urinary changes. In case 2, which was studied from onset to death, the urinary changes developed only during the last few months of the patient's life. In a comprehensive survey of this subject, Ellis [12] pointed out that

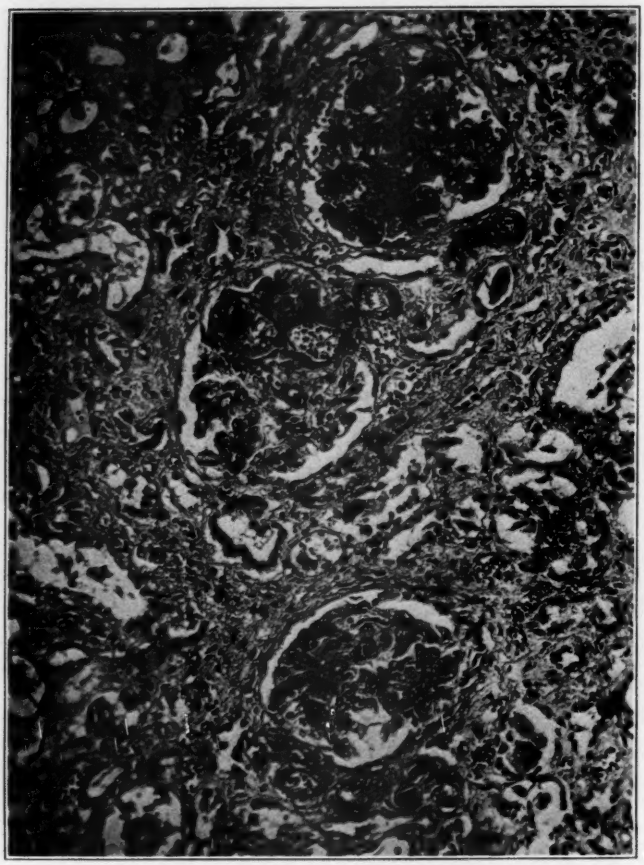

Fig. 2.—Section showing arteriolonecrosis of the preglomerular arteriole on the right side of the photograph. It shows extravasation of red cells outside of the vessel as well as of many red cells in Bowman's space. Great thickening, smudginess and tinctorial change are represented in all three of the glomeruli. Such changes in the tufts, however, are usually focal.

12. Ellis, A.: Malignant Hypertension, Lancet **1**:977-980 (April 23) 1938.

urinary changes are later manifestations and that in 5 of 40 patients albuminuria did not develop until later in the disease.

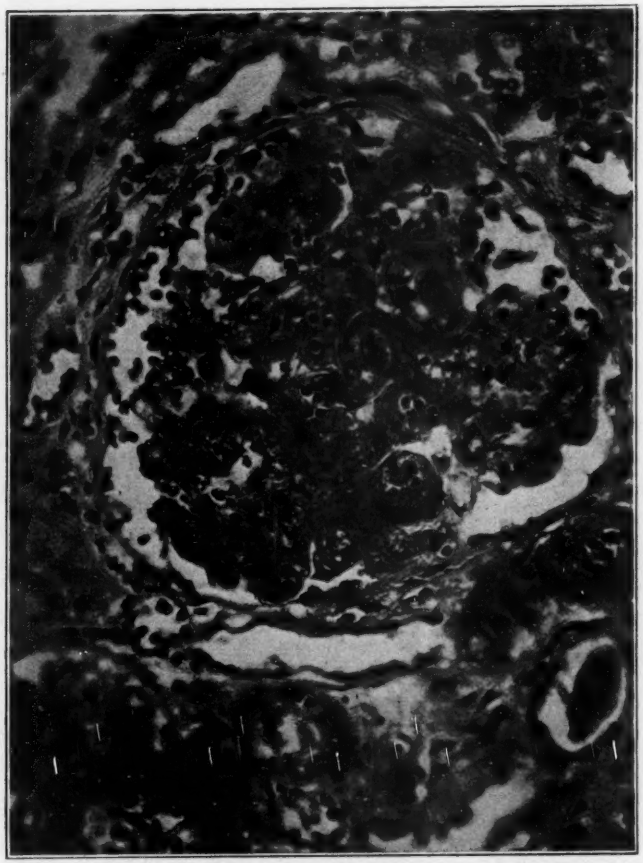

Fig. 3.—High power magnification of a glomerulus of malignant hypertension, showing swollen endothelial nuclei and granular stippling of the arteriolar wall. There is also necrosis and smudginess of the upper half of the glomerulus, which shows free red cells in Bowman's space.

Perhaps most unusual of all courses of malignant hypertension is the exceptional instance of spontaneous remission, as illustrated in case 3. Formerly it was believed that once the signs and symptoms of malignant

hypertension came above the threshold of clinical recognition, the expectancy of life was from eighteen to thirty months. This opinion, of course, must be modified, as many patients live much longer than this and the

Fig. 4.—Section of myocardium, showing area of necrosis with extravasation of red cells. A few polymorphonuclear leukocytes are also in the area of necrosis. Such cellular reaction, however, is usually sparse.

development of small remissions is possible, which factors increase the life expectancy considerably. There have been other reports of cases

with spontaneous remissions,[13] but the case reported here is one of almost complete remission for a period of over twelve years. As shown from the case report, the patient had the fully developed syndrome of malignant

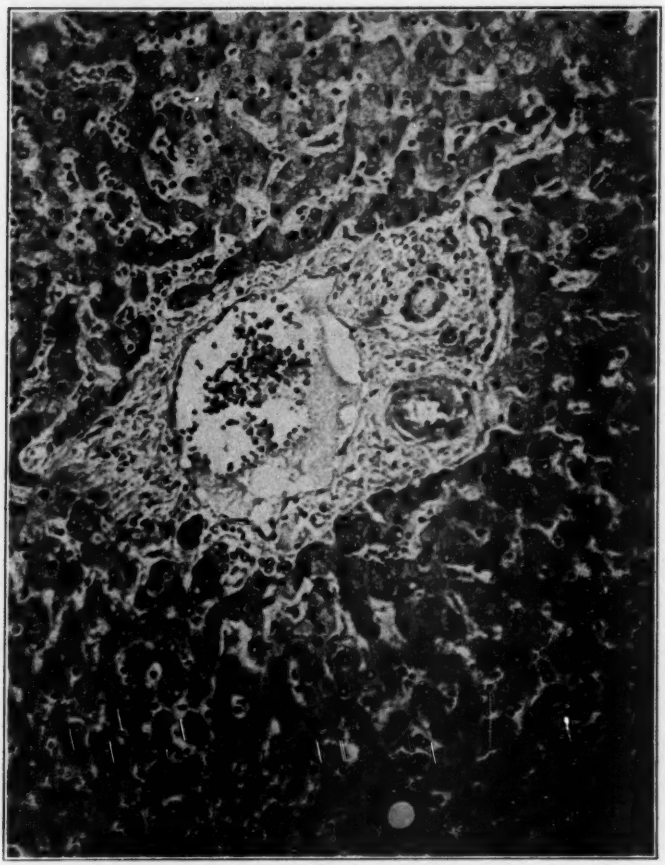

Fig. 5.—Portal zone of liver, showing the greatly dilated portal vein and the irregularity in the intensity of staining of the arteriole.

13. Wagener, H. P., and Keith, N. M.: Diffuse Arteriolar Disease with Hypertension and the Associated Retinal Lesions, Medicine **18**:317-430 (Sept.) 1939.

hypertension, the diagnosis being confirmed by several authorities. With nothing but routine treatment the remission set in. This remission was characterized by a fall in blood pressure, at times almost to normal levels,

Fig. 6.—Interlobular zone of the pancreas, showing several large arterioles with complete necrosis of the vessels and obliteration of the normal outline of the lumen.

by subsidence of headache, visual disturbances and anorexia and by abatement of azotemia, albuminuria and hematuria. Most important of all, there has been a return of physical well-being.

The course of malignant hypertension becomes modified by heart failure, by cerebral disturbances, including apoplexy, and finally by renal insufficiency and uremia. The kind of heart failure is always the same,

Fig. 7.—Section of pericardium, showing a loose histiocytic reaction of the fat zone with masses of fibrin on the surface. This fibrinous pericarditic deposit was encountered in approximately one third of the cases.

i. e., failure of the left ventricle with pulmonary congestion. In our series 14 of the 33 patients on whom autopsy was performed had heart failure, though only 8 actually died of heart failure.

Regarding our observations on the course of malignant hypertension, it becomes aparent that the term "malignant" does not always connote the same thing to all observers. This is particularly true when one is

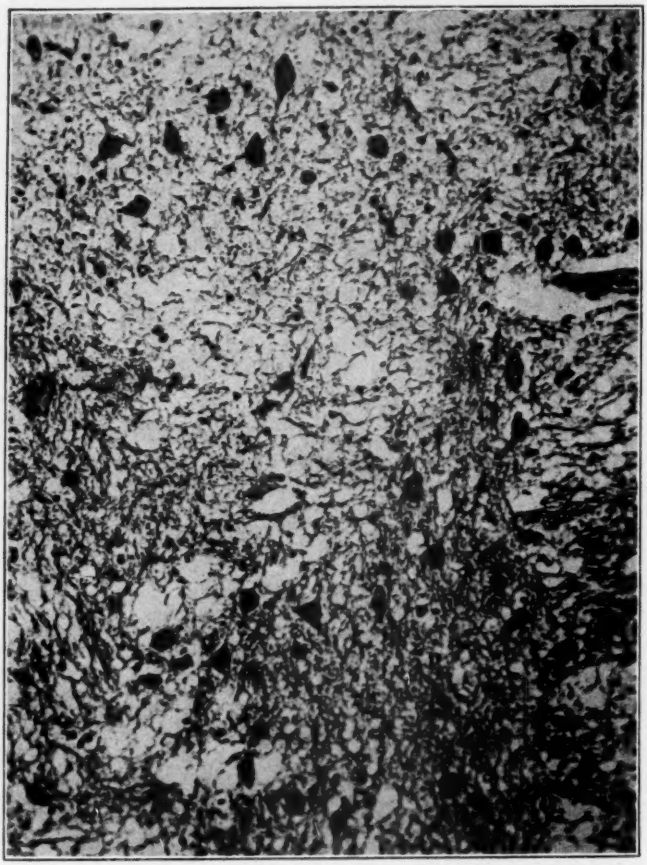

Fig. 8.—Section of brain, showing disorganization of the cerebral tissue, with loose-lying neurons and marked vacuolization of the brain tissue.

dealing with the patient in the transitional stage, when all features of malignant hypertension are not yet present but the case is one of malignant hypertension. In this situation it is apparent that malignant hyper-

tension fails in many cases to present the uniform picture looked for as the classic indication of the disease.

COMMENT

The use of the term "malignant" to identify a phase or a form of hypertensive cardiovascular disease has become so well rooted in medical literature that it seems better to understand the various connotations of the term than to hope for its disuse, as we did formerly.

It was believed that the stage of malignant hypertension represented the result of the addition of some factor, as a superimposed infection, to the condition of a kidney already damaged by arteriosclerosis. Subsequently Volhard [14] postulated that the kidney of benign hypertensive cardiovascular disease may secrete a substance which constricts arterioles and converts benign hypertensive cardiovascular disease into the acute (malignant) form. He emphasized that, contrary to the former opinion, he was of the belief that malignant hypertension may develop without the occurrence of the previous benign form.

If malignant hypertension may develop without the previous benign form it must be a rare occurrence, as this was noted in only a few of the cases in the present review. The cause of the conversion of the benign type into malignant hypertension is not known, but the work of Volhard,[14] Goldblatt [15] and Page and Corcoran [16] goes to show, experimentally at least, that moderate constriction of renal arteries leading to altered renal blood flow produces benign hypertensive cardiovascular disease and that further constriction brings on the malignant phase. This experimental work regarding the cause of malignant hypertension is significant from the clinical viewpoint.

The state of hypertensive cardiovascular disease preceding the clinical manifestations of the malignant form may be of very short duration. Some yet unknown factor added to the state of benign hypertensive cardiovascular disease at any time during its development produces the additional features of the disease which is called malignant hypertension. It is not surprising, therefore, that in some instances malignant hypertension may be preceded by hypertensive cardiovascular disease for many years or for a matter of a few months. The unknown factor which acts in the instances of benign arteriolosclerosis is particularly active in

14. Volhard, F.: On the Pathogenesis of Red (Essential) Arterial Hypertension and of Malignant Nephrosclerosis, Stanford M. Bull. **6**:13-28, (Feb.) 1948.

15. Goldblatt, H.: The Renal Origin of Hypertension, Monograph in American Lectures in Pathology, Publication no. 14, American Lecture Series, Springfield, Ill., Charles C Thomas, Publisher, 1948.

16. Page, I. H., and Corcoran, A. C.: Arterial Hypertension: Its Diagnosis and Treatment, Chicago, The Year Book Publishers, Inc., 1945.

the kidney, promoting a very rapid rate of progressive arteriolosclerosis, which so frequently is accompanied with uremia. The state of hypertensive cardiovascular disease and uremia then produces arteriolonecrosis, which so commonly is irreversible. That some arteriolonecrosis may be seen in terminal benign hypertensive cardiovascular disease with uremia suggests that malignant hypertension is a similar entity but one which progresses at a much more rapid rate. The factor which introduces arteriolonecrosis is not understood. The alteration in tissue metabolism in the state of renal insufficiency added to preexisting disease of a vessel (arteriolosclerosis) may account for necrosis. The possibility of an antigen-antibody reaction taking place in the vessel cannot be confirmed or denied. Certainly the necrotic features resemble very closely the collagen changes of diseases such as rheumatic fever, polyarteritis, lupus erythematosus, etc., which are generally thought to be states of altered reaction or of hypersensitivity.

With recent advances in experimental pathology and in neurosurgery, the differentiation of malignant hypertension and chronic glomerulonephritis becomes of more than academic interest. It is becoming more generally accepted that malignant hypertension is a later phase or stage of benign hypertensive cardiovascular disease. Not only is this the conclusion of special investigators, but it also is the opinion held by clinicians who have studied their patients from the onset of symptoms to death. If these cases are recognized in the earliest stages, that is, in the stage of transition before the end stage develops, sympathectomy or other treatments applied vigorously may bring about abatement of the disease and prolong life, even though complete cure is only a hoped-for result at the time of this report.

Patients with chronic glomerulonephritis show a tendency to remissions of long duration. Unlike malignant hypertension, in which the course is usually downward from the start, a series of remissions and setbacks covering a period of years characterize chronic nephritis.

Page and Corcoran [17] pointed out several facts which aid in the differential diagnosis. In chronic glomerulonephritis, in contrast to malignant hypertension, there is a low rate of glomerular filtration, diminished secretory capacity of the tubules and a higher rate of proteinuria. In addition, in advanced glomerulonephritis hypoproteinemia occurs as a result, in part, of excessive albuminuria, whereas it is rarely found in malignant hypertension.

The kidney is the chief organ showing involvement in chronic nephritis, and large quantities of abumin, many casts, and red cells are

17. Corcoran, A. C., and Page, I. H.: Differential Diagnosis of Terminal Glomerulonephritis and Malignant Hypertension, Ann. Int. Med. **21**:747-764 (Nov.) 1944.

present, though blood pressure is not likely to be so greatly elevated as in malignant hypertension. Severe anemia is also a point in favor of chronic nephritis.

All the essential organs of the body except the lungs are involved in the course of malignant hypertension, although the heart and the vascular system predominate. Heart disease, which is not a usual finding in chronic nephritis, is common in malignant hypertension, and less than 3 to 4 Gm. of albumin in the urine in twenty-four hours is characteristic of excessive hypertensive cardiovascular disease.

Another condition frequently mistaken for malignant hypertension because of the similarity of symptoms is tumor of the brain. Palmer, Nyssens and White [18] recently compared the symptoms, signs, and findings in the spinal fluid in 30 patients with severe hypertensive cardiovascular disease and papilledema, in 25 patients with proved brain tumor and in 15 patients with severe hypertensive cardiovascular disease but without papilledema. They found that the most important differential characteristic is the slow, steady progression of neurologic localizing signs in brain tumor. From our own experience we have found hypertensive cardiovascular disease an uncommon feature in patients with brain tumor. A study of the onset and clinical course of the disease as well as careful studies of the kidney will help to make the differentiation, and when brain tumor is suspected special methods, such as air encephalography, should be employed.

The correct diagnosis of malignant hypertension can usually be made by a careful study of the history of the patient and the use of simple tests of renal function.

TREATMENT

It is one of our aims in presenting this paper to emphasize the importance of recognizing malignant hypertension at the earliest stages when the conversion from the benign to the malignant form of the disease has begun to take place. It appears to us that radical sympathectomy is warranted when this early diagnosis is made. Recently Peet and Isberg [19] reported the results of this operation in 143 cases of malignant hypertension and declared that this treatment offers some hope if applied early. Thirty-one of 143 patients with malignant hypertension survived five years after operation, representing a survival rate of 21.6 per cent. Twenty-three patients were still living five to twelve years after operation.

18. Palmer, R. S.; Nyssens, A. F., and White, J. C.: Severe Hypertension with Papilledema Simulating Brain Tumor: Differential Diagnosis and Treatment, New England J. Med. **239**:322-327 (Aug. 26) 1948.

19. Peet, M. M., and Isberg, E. M.: The Problem of Malignant Hypertension and Its Treatment by Splanchnic Resection, Ann. Int. Med. **28**:755-767 (April) 1948.

Harland and d'Abreau,[20] in a review of 24 cases of severe hypertension, also reported that lumbothoracic sympathectomy causes great symptomatic relief and that the malignant phase in primary malignant hypertension may disappear.

As regards medical treatment, much controversy has arisen regarding the place of the rice diet in malignant hypertension. Schroeder and others [21] stated that diets low in salt, protein or calories are preferable to the rigors of the rice diet. They pointed out that the regimen advocated by Kempner has at least four factors which need evaluation: The diet is low in protein, low in fat, low in salt and has a strong psychotherapeutic influence. In addition, Kempner reported no control periods in his studies.

Recently Kempner [22] published a report on a patient with malignant hypertension who was treated successfully with the rice diet. This report, however, showed some of the difficulties involved in using the diet and indicated the serious dangers which may result if these difficulties are not dealt with correctly.

Our experiences with lumbar sympathectomy have been similar to those of the authors previously referred to. If lumbar sympathectomy is performed early in the course of malignant hypertension, especially in a younger person, the results are likely to be more satisfactory than if carried out late in the course of the disease or in older persons in whom the arteriosclerotic process is advanced.

Other than sympathectomy, general measures of treatment were carried out which were directed toward the system involved. All patients were placed on a diet low in sodium (1,000 mg. or less daily). Although the low sodium diet seemed to have no appreciable effect of lowering the blood pressure, it was felt that it did aid in the prevention and treatment of heart failure. In one instance, the diet had to be discontinued because of associated hyperkaliemia.

When heart failure persisted the patients received treatment directed specifically to it, i. e., the administration of digitalis, oxygen, aminophylline or mercurial diuretics. In our experience, the persistent use of mercurials at periodic intervals after the patient recovered from the first episode of failure was very helpful in preventing or delaying further episodes of failure.

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20. Harland, J. C., and d'Abreau, F.: Lumbodorsal Sympathectomy in Severe Hypertension: An Interim Survey, Brit. M. J. **1**:1019-1024 (June 11) 1949.

21. Schroeder, H. A.; Futcher, P. H., and Goldman, M. L.: The Effects of the "Rice Diet" upon the Blood Pressure of Hypertensive Individuals, Ann. Int. Med. **30**:713-732 (April) 1949.

22. Kempner, W.; Peschel, E., and Starke, H.: Rice Diet in Malignant Hypertension: A Case History, Am. Pract. **3**:556-563 (May) 1949.

Hypertonic dextrose solution was found to be rather helpful as a diuretic and in relieving severe headache due to cerebral edema. Fifty per cent dextrose solution was used intravenously in amounts varying from 50 to 300 cc.

Magnesium sulfate was helpful in lowering the blood pressure when given in a 10 per cent solution in doses of 10 to 20 cc. intravenously or intramuscularly several times daily.

The treatment of uremia was not very successful since it almost always appeared terminally. Fluids were administered parenterally according to the blood values for sodium, chlorides, carbon dioxide-combining power and total and fractional protein. Sodium-free serum albumin was given in doses of up to 50 Gm. a day without any noticeable effect.

Our experiences with the treatment of patients with malignant hypertension correspond closely to those of workers who have made similar observations. Very little can be hoped for when the disease reaches its end stage. However, in the earlier phases, vigorous treatment by radical measures is advocated.

SUMMARY

1. Thirty-nine cases of hypertensive cardiovascular disease (acute) —often called malignant hypertension—studied clinically and at autopsy are presented so that a clearer clinical and pathologic picture may be seen and in order to emphasize the importance of early recognition and prompt treatment.

2. Special emphasis is placed on those cases showing certain exceptions in the clinical course, such as a case of spontaneous remission, a case in which the classical changes of malignant hypertension were lacking from the eyegrounds and 1 case in which the cardinal changes developed before the onset of albuminuria and other evidences of renal disease.

3. An analysis of the clinical data is presented with particular attention to the heart, the kidneys and the blood pressure. The duration of illness and the cause of death are discussed.

4. The chief pathologic findings showed the kidneys, heart, liver, spleen, pancreas and adrenal glands to be commonly involved. The characteristic vascular lesion was that of arteriolonecrosis.

5. The natural history and course of malignant hypertension are reviewed and show that some cases do not present the classical picture of the disease. The indications of the conversion from the benign form of hypertensive cardiovascular disease to malignant hypertension are reviewed, as well as the rare exceptions in the clinical course.

6. The differentiation of chronic glomerulonephritis and brain tumor from malignant hypertension is discussed, and it is stressed that the correct diagnosis of malignant hypertension can usually be made by a careful study of the history of the patient and the use of simple tests of renal function.

7. When an early diagnosis of malignant hypertension is made, radical sympathectomy is warranted. Early surgical treatment, especially in younger persons, is likely to be more satisfactory than that carried out late in the course of the disease or when the arteriosclerotic process is advanced.

ACUTE PORPHYRIA

Report of a Case

CHARLES H. GRAY, M.B.
LONDON, ENGLAND

ACUTE porphyria is a familial metabolic disease of unknown etiology characterized by repeated attacks of severe abdominal colic, associated usually with constipation and often with vomiting, and accompanied with abnormalities of the central nervous system amounting in many cases to rapidly fatal ascending paralysis. It has generally been thought that an essential feature of the condition is the passage of red urine containing an excess of porphyrins and other pigments, but recently it has become appreciated that these pigments are frequently excreted in the form of a colorless precursor. Waldenström and Vahlquist (1939)[1] gave this precursor the name porphobilinogen and claimed that, whereas it is stable in alkaline solution, in acid solution it is converted to uroporphyrin and to a urobilinoid pigment, porphobilin. This was confirmed by Prunty (1945).[2] The present paper describes a fatal case of porphyria, the clinical features of which were typical of the condition in every way, but in which the urine practically never contained any gross excess of preformed porphyrins but always contained large amounts of the colorless porphobilinogen. On standing the urine darkened visibly with the formation of dark brown and red pigments, including the so-called ether-insoluble uroporphyrin III.

REPORT OF CASE

The patient, an unmarried woman of 23 serving in the Auxiliary Territorial Service, was admitted under the care of Dr. Philip Ellman to Leatherhead Emergency Hospital on July 4, 1945, with retrosternal and abdominal pain, vomiting, and weakness of the back, all of about three weeks' duration. She had enjoyed good health until the present illness. The symptoms began abruptly after bathing and sun bathing one afternoon in the middle of June, when soreness in the chest and an aching pain in the subumbilical region rapidly developed and persisted with such severity as to interfere with sleep. The following day vomiting

From the Biochemical Department, King's College Hospital.

1. Waldenström, J., and Vahlquist, B.: Studien über die Entstehung der roten Harnpigmente (Uroporphyrin und Porphobilin) bei der akuten Porphyrie aus ihrer farblosen Vorstufe (Porphobilinogen), Ztschr. f. physiol. Chem. **260**: 189, 1939.

2. Prunty, F. T. G.: Acute Porphyria: Some Properties of Porphobilinogen, Biochem. J. **39**:446, 1945.

began and progressed so that she was able to retain no solid food and lost 14 pounds (6.4 Kg.) in weight during the two weeks prior to admission. There was severe constipation during that time. For a few days prior to admission she complained of weakness, especially of her back, so that she had difficulty in sitting up in bed.

Physical Examination.—On examination, the patient appeared to be acutely ill, the temperature was 98.8 F., and the pulse rate was 108 but regular and of good volume. The blood pressure was 132 systolic and 86 diastolic. The pupils were dilated but reacted to light and in accommodation. The tongue was furred and the abdomen soft and without tenderness. Rectal examination revealed no abnormality. No abnormality could be found in the respiratory system, the cardiovascular system or the central nervous system. The reflexes were all present, and the plantar reflexes were flexor in type. A blood count showed hemoglobin concentration (Haldane) of 100 per cent and 10,000 white blood cells per cubic millimeter (76 per cent polymorphs, 22 per cent lymphocytes, 1 per cent monocytes, 1 per cent eosinophils and no basophils). The erythrocyte sedimentation rate was 10 mm. in one hour. Microscopic examination of the urine revealed no abnormality. Fluoroscopic examination after a barium sulfate meal showed a normal stomach and duodenum, but there was tenderness over the cecal area. The benzidine test was persistently negative for occult blood. No abnormal shadows were seen in the lung fields. On July 16, the patient was seen by Mr. S. G. Clayton, F.R.C.S., who reported that he could find no gynecologic abnormalities.

Laboratory Examination.—On August 3 the ward sister noticed that a specimen of urine had turned pink on standing overnight, and a fresh specimen was sent to the laboratory for examination. This specimen was of normal color and contained no bilirubin and no excess urobilin, as determined by Schlesinger's test, but gave a very strongly positive reaction to Ehrlich's reagent. The association of this positive reaction with a negative reaction in the Schlesinger test was highly suggestive of the presence of porphobilinogen. On repeating Ehrlich's test with the modified reagent of Watson and Schwartz (1941),[3] the red pigment was insoluble in chloroform, thus confirming the presence of porphobilinogen. The original specimen was therefore reexamined spectroscopically, but no abnormal absorption bands could be seen in a layer 5 cm. thick. On acidification of 25 cc. of urine with acetic acid, extraction with ether and extraction of the ether extract with 2 cc. of 5 per cent hydrochloric acid solution, the acid layer became pink in color and showed the typical acid absorption band of a porphyrin. The diagnosis of acute porphyria was thus established; further specimens of urine were examined more fully, as detailed in the section on special chemical investigation.

Course.—On August 6 the patient was taking a little solid food, but the weakness was becoming worse; she then had severe abdominal pain in the umbilical region. Apart from flaccidity and weakness of all muscles, no abnormal signs in the central nervous system could be found. The pulse rate was rapid (128 beats per minute). The heart was not enlarged, nor could any murmurs be heard. A few rhonchi and rales could be heard. On August 8 Dr. Worster-Drought examined the central nervous system and reported as follows:

"The pupils were slightly dilated, reacting sluggishly to light but normally in accommodation; other cranial nerves were normal. There was general loss of power in the arms without actual paresis. The arm jerks were moderately brisk

3. Watson, C. J., and Schwartz, S.: A Simple Test for Urinary Porphobilinogen, Proc. Soc. Exper. Biol. & Med. **47**:393, 1941.

and were equal, but the muscles were tender. All movements were present in the legs but there was general loss of power, the muscles being generally atonic. The leg muscles were tender. The knee jerks and abdominal reflexes could not be elicited, but the ankle jerks were present, though sluggish, and the plantar responses were flexor in type. Vibration sense in the arms and legs was present but somewhat diminished. Skin sensation was fairly normal over the legs but was impaired over the arms and the greater part of the trunk. The clinical manifestations were those of peripheral neuritis."

By August 13 the attacks of abdominal pain were lasting about an hour and occurring regularly every five or six hours. The urine output had fallen to 300 cc. per day, and it was thought worth while to try alkali therapy. Twelve hundred cc. of 6 per cent sodium bicarbonate solution followed by 500 cc. of physiologic sodium chloride solution was then given intravenously, after which a strong alkaline mixture was given by mouth every four hours. At that time the general condition of the patient improved considerably, vomiting became less frequent and she began eating and drinking better, so that the urine output remained higher than before alkali therapy was given. At that time the white cell count was 20,000 per cubic millimeter, of which 89 per cent were polymorphonuclear leukocytes. The patient was found to have a purulent vaginal discharge, which on microscopic examination revealed many Trichomonas vaginalis organisms and culture of which yielded a strong growth of Streptococcus faecalis and of diphtheroids. The condition was effectively treated with pessaries of acetarsone (stovarsol®) and lactic acid douches. Reexamination of the central nervous system by Dr. Worster-Drought revealed the following: "The cranial nerves were still normal. The motor weakness in the arms was more pronounced than at the previous examination, amounting to definite paresis. The arm jerks were absent except for slight bilateral brachioradialis jerks. Both knee and ankle jerks were absent, but there was rather better motor power in the legs, with no paresis. The muscles generally were flabby and atonic. Sensation to pinprick and to cotton was much impaired over the arms, neck and trunk and the upper part of the thighs. Sensation was normal below the upper part of the thighs."

On August 27 the patient was depressed and mentally confused, with the abdominal pains as severe as ever. The weakness of the limbs was more pronounced. The urine was alkaline, and the output was again only 300 cc. daily. She was therefore given, intravenously, 4 liters of 4.1 per cent glucose solution in 0.16 per cent saline solution followed by 500 cc. of 6 per cent sodium bicarbonate solution, but the response was less dramatic than on the previous occasion. On August 29 Dr. Worster-Drought reported again: "The condition was worse. The arms were almost completely paralyzed (there were no movements in the hands), and all reflexes were absent except the brachioradialis jerks. There was paresis of the spinal muscles and those of the posterior portion of the neck, and possibly of the tongue and the muscles of deglutition. The process was affecting the bulbar cranial nerves. Paresis of the legs was more profound, especially below the knee, but movements were still present in the muscles of the thighs. The sensory changes were more widespread."

On August 30 the voice was weak and the patient was taking no solid food, although she was able to drink well. The bowels had been obstinately constipated and relieved with occasional enemas. The patient was now partially incontinent of urine. The pulse rate remained regular at 120 to 140, although the blood pressure was well sustained at 120 systolic and 90 diastolic. The heart was not enlarged. The intake of air was poor, and although the upper intercostal muscles were working well, there appeared to be paralysis of the lower intercostal

muscles and of the diaphragm. On August 31 the lower intercostal muscles and the diaphragm were quite paralyzed, as was the orbicularis oculi. Pinprick sensation was absent over the face and arms but present over the legs. There appeared to be early recurrent laryngeal paralysis, as the voice was becoming weaker, although the palate elevated equally on both sides. Although the patient had passed no urine for twenty-four hours, the bladder was not distended; later in the day she passed about 250 cc. of urine. At 11 a. m. she was put in a Drinker respirator, in view of the progressing respiratory paralysis. On September 1 she complained of nausea, although there was no actual vomiting. The following day there were rales on both sides of the chest and the temperature was 102 F.; this was the only hyperpyrexia throughout the illness. It was clear that hypostatic pneumonia had developed in spite of periodic alteration of the patient's position in the lung, and she was then given 20,000 units of penicillin G every four hours. The temperature was normal by September 3, but she was unable to swallow. She was then given frequent small feedings of milk through a stomach tube passed intranasally, but she died at 4 p. m. on September 5.

Treatment throughout had been symptomatic. The abdominal pains had not been allayed by various barbiturates which had been given prior to the establishment of the diagnosis and could only be allayed by repeated intramuscular injections of pethidine hydrochloride (the name used in "The British Pharmacopœia" for meperdine hydrochloride).

Postmortem Examination (by Dr. David Nabarro).—The body was that of a wasted girl; there was no superficial abnormality. Both pleural cavities contained a little free fluid. Both lungs showed marked consolidation due to confluent bronchopneumonia, involving especially the upper and middle lobes of the right lung and the upper lobe of the left lung. The surface of the left lung showed a few scattered flakes of fibrin. The tracheal cartilages seemed a little soft, but otherwise there was no abnormality. The lymph node at the bifurcation of the trachea was enlarged and dark. The esophagus was normal. The pericardium contained a very little free fluid. The heart and the great vessels were normal. The abdominal cavity contained no free fluid. The liver weighed 945 Gm. and appeared soft and reddish brown in color. The spleen was not enlarged. The intestinal tract and the pelvic organs appeared normal. The histologic examination of the organs showed no abnormalities except pneumonic changes in the lungs and slightly cloudy swelling of the liver with early fatty degeneration. There was no excess of pigment in the liver, nor was there any deposit of the orange-red and golden granules described by Prunty (1946).[4]

Fluorescence Studies of Organs.—At autopsy, various small pieces of tissue were examined in ultraviolet radiation for fluorescence before and after boiling for five minutes in a small quantity of dilute hydrochloric acid. Tissue from the lungs, spleen, thyroid, ovary, intestine and thymus and from muscle showed no red fluorescence either before or after heating with acid. In the case of tissue from the heart muscle, the adrenal gland and the kidney the hydrochloric acid acquired red fluorescence after heating with the tissue; this was especially true of the kidney. The liver fluoresced a dull green before and after heating with acid, but after treatment the acid acquired a faint red fluorescence considerably weaker than that

4. Prunty, F. T. G.: Acute Porphyria: Investigations on Pathology of Porphyrins and Identification of Excretion of Uroporphyrin I, Arch. Int. Med. **77**:623 (June) 1946.

obtained with the kidney. The cut surface of the untreated costal cartilage and tracheal cartilage presented a ring of red fluorescence. The dura lining the inner table of the parietal bones also showed an area of fluorescence.

Porphobilinogen Content of Organs.—The porphobilinogen content of the liver, kidney, spleen and muscle was determined by the method of Prunty (1945).[2] The spleen and muscle contained practically none, but the liver and kidney contained 16.5 and 103 units respectively per hundred grams of tissue, corresponding to 154 and 287 units respectively for the whole organs.

Quantitative Determination of Urinary Porphyrins.—From August 4 till the day of death daily determinations of the urinary excretion of coproporphyrin and uroporphyrin were made by the methods of Rimington (1943).[5] From August 14 the porphobilinogen excretion was determined by the method of Prunty (1945) [2] almost every day till death. The chart records the results together with the average pulse rate. The measurements of porphobilinogen were made within a few hours of the completion of collections of the twenty-four hour specimens, but the determinations of porphyrin in many instances were necessarily delayed until a few days after the patient's death. The urine specimens were stored in the refrigerator.

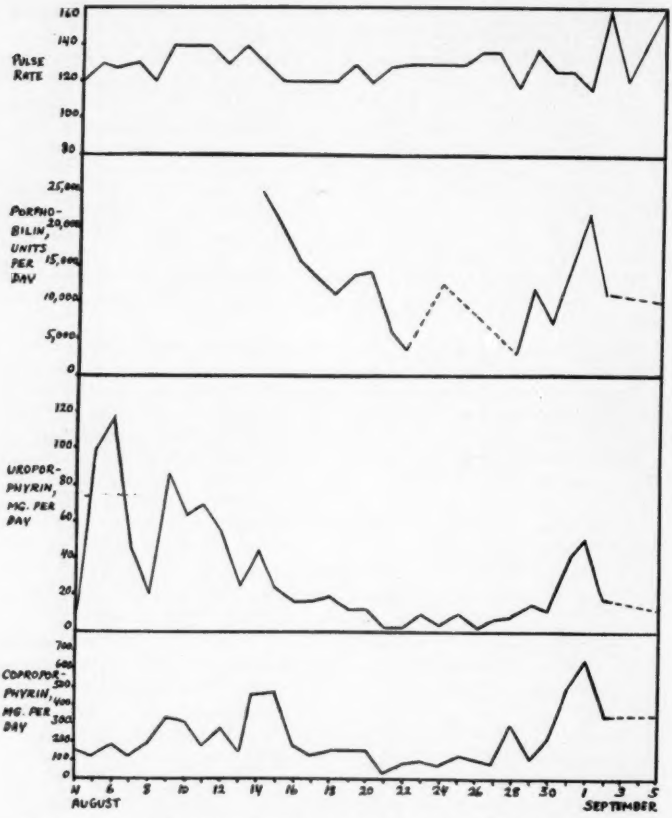
Obstinate constipation rendered quantitative determination of fecal porphyrin of little value; the few specimens obtained were therefore used for isolation of the pigments.

Special Chemical Examination.—Urine: Ether-soluble porphyrin: Two thousand cubic centimeters of urine were acidified with 200 cc. of acetic acid and extracted successively with two 1,000 cc. quantities of ether. The ether extracts were washed with water and extracted with 5 per cent hydrochloric acid solution. After neutralizing with saturated potassium acetate, the porphyrin was again transferred to ether. The ether extract was washed three times and then evaporated to dryness. After esterification of the extract overnight with methyl alcohol saturated with hydrochloric acid gas the porphyrin ester was diluted with ice water and transferred to chloroform. The chloroform solution was washed with water, 10 per cent ammonia solution and again with water and then evaporated to dryness. On crystallization from chloroform and methyl alcohol, the typical curved needle crystals of coproporphyrin I tetramethyl ester were obtained. The melting point was 288 C.; however, the amount obtained was too small for recrystallization.

Ether-insoluble porphyrin: Two hundred cubic centimeters of ether-extracted urine, which on standing rapidly became red-brown in color, was adjusted to p_H 3.2 with concentrated hydrochloric acid, and the solution was extracted once with 200 cc. and four times with 100 cc. of ethyl acetate. The ethyl acetate extract was then extracted four times with 10 per cent hydrochloric acid solution. The united hydrochloric acid extracts were adjusted to p_H 3.2 with 40 per cent sodium hydroxide solution, and the solution was left at 4 C. (39.2 F.) overnight. The bulk of the porphyrin precipitated out and was centrifuged off, washed twice with 2 per cent acetic acid solution and dried *in vacuo*. After esterification with methyl alcohol–hydrochloric acid and working up in the usual way, the crude porphyrin ester was recrystallized five times from chloroform and methyl alcohol. Four and a half milligrams of hairlike crystals typical of Waldenström's uroporphyrin III methyl ester were obtained. These crystals melted at 261 C., with

5. Rimington, C.: A Simple Fluorescence Comparator and Its Application to the Determination of Porphyrins, Biochem. J. **37**:137, 1943; A Quantitative Method for the Determination of Uroporphyrin in Pathological Urines, ibid. **37**:443, 1943.

slight softening at 258 C. On working up the mother liquors a further 2 mg. of these crystals was obtained. Thus, the total yield corresponded to 32.5 mg. per liter of urine. (When a sample of the same coproporphyrin-free urine was worked up by the method of Grinstein, Schwartz and Watson (1945),[6] involving absorption on talc followed by combined elution and esterification with methyl alcohol hydro-



Various data in the reported case of acute porphyria, including pulse rate and excretion of urinary porphyrins and porphobilinogen.

chloric acid, similar crystals with a melting point of 262 to 266 C., were obtained in a yield corresponding to 30.6 mg. per liter of urine.)

6. Grinstein, M.; Schwartz, S., and Watson, C. J.: Studies of the Uroporphyrins: I. The Purification of Uroporphyrin I and the Nature of Waldenström's Uroporphyrin, as Isolated from Porphyria Material, J. Biol. Chem. **157**:323, 1945.

A small sample of the ester obtained from the ethyl acetate extract of the urine was subjected to further examination. The material was reesterified, and immediately after transfer to chloroform the chloroform solution was taken to dryness and the residue taken up in benzene and run through a 1.5 by 15 cm. column of calcium carbonate. Apart from two very small zones at the top of the column the porphyrin ester passed through the column as an entity. After five recrystallizations the melting point was 264 to 266 C. Part of this material was subjected to decarboxylation according to the method of Grinstein, Schwartz and Watson (1945).[6] Coproporphyrin I ester (melting point 245 C.) was readily isolated from the decarboxylation product together with approximately an equal quantity of a porphyrin ester of a melting point of 233 to 234 C. and with an alpha absorption band at 623.6 millimicrons in chloroform.

Feces: A total of 360 Gm. of feces was available for investigation. The feces showed no gross red fluorescence in ultraviolet rays, although they were extremely dark in color. There were, however, a number of small areas showing intense white fluorescence, and for this reason only 330 Gm. were used for isolation of the porphyrins, the remaining 30 Gm. being investigated for the presence of myobilin, as explained in the section on that substance.

Porphyrins: The feces were exhaustively extracted with ether and acetic acid until the final washings were practically colorless. The ether-extracted residue was then allowed to dry, while the ether extract (total volume 1,750 cc.) was concentrated to 150 cc. and then poured into 1.5 liters of 1 per cent hydrochloric acid solution. After standing overnight the surface layer of pigmented fatty material was filtered off and the filtrate neutralized to congo red with saturated solution of potassium acetate and then extracted with ether. (An attempt to prepare crystalline stercobilin from the ether-extracted aqueous phase was unsuccessful.) The porphyrin was then transferred from the ether extract to 5 per cent hydrochloric acid solution and then back into ether again after neutralizing with potassium acetate. The ether was evaporated off and the dry residue esterified with methyl alcohol saturated with dry hydrogen chloride. After standing overnight at 4 C. the solution was diluted with ten times its volume of water and the porphyrin quantitatively extracted with chloroform. The chloroform solution, after being washed twice with water and 10 per cent ammonia solution and three times more with water, was filtered through a chloroform-moistened filter paper and evaporated to dryness. The dry residue was then purified by chromatography from benzene through a column of alumina. After two recrystallizations typical crystals of coproporphyrin I methyl ester were obtained. The yield was 1.5 mg. and the melting point 252 C.

Ten grams of the ether-extracted fecal residue (total weight, 30 Gm.) was worked up by the method of Grinstein, Schwartz and Watson (1945),[6] and a further very small quantity of coproporphyrin I ester of 248 to 253 C. melting point was isolated together with 1.4 mg. of typical hairlike crystals of uroporphyrin I methyl ester. After four recrystallizations these melted at 278 to 280 C.

Myobilin: Because of the areas of white fluorescence observable in ultraviolet radiation, 30 Gm. of the extracted feces were used for the attempted isolation of myobilin by the method of Meldolisi, Siedel and Möller (1939),[7] but no material was obtained with properties corresponding to those described by those workers.

Bile: About 5 cc. of yellow bile was available for investigation. Although crystalline esters of porphyrins have been readily isolated from such quantities of

7. Meldolisi, G.; Siedel, W., and Möller, H.: Ueber Myobilin, Ztschr. f. physiol. Chem. **259**:137, 1939.

bile in other cases of porphyria, no esters of porphyrins appeared to be present in this case. Instead there was obtained a red pigment, soluble in ether and possessing only general absorption at the blue end of the spectrum. This was transferred to 10 per cent hydrochloric acid solution when the color changed sharply to blue (there were no definite absorption bands), presumably owing to formation of hydrochloride. The quantity of pigment was insufficient to permit its isolation.

Organs: Samples of liver, kidney, spleen and muscle were separately investigated for the presence of porphyrin. The finely minced tissues were ground up repeatedly with a mixture of ether (20 volumes) and acetic acid (1 volume). The ether extract was worked up in the usual way for ether-soluble porphyrins, and the ether-extracted tissues were examined for ether-insoluble porphyrins by the method of Grinstein and others.[6] Apart from traces of protoporphyrin, which were not isolated, only the liver and the kidney contained significant quantities of porphyrins. From both of these organs coproporphyrin I was obtained (the melting point of the methyl ester was 251 C.). No ether-insoluble porphyrins could be detected in any of the organs, although, by a similar technic, uroporphyrin I was readily isolated from the liver in another fatal case of acute porphyria. In that case the whole liver fluoresced a brilliant red in ultraviolet rays and was quite different in its behavior from the liver in the present case.

Cytochrome, Myoglobin and Catalase: Dr. E. F. Hartree examined samples of muscle for cytochrome and myoglobin and samples of liver for activity of catalase. He reported that "cytochrome and myoglobin in the muscle were not below average. The myoglobin level appeared, if anything to be high (it was 15 mg. per gram wet weight of tissue, as against the more usual 10 mg.); however, variations can be great among individual persons, both in myoglobin and in cytochrome. Hepatic catalase showed normal activity."

Preparation of Porphobilinogen: A solution of porphobilinogen in concentrated solution was prepared by the method of Prunty (1945).[3] In acid solution porphobilinogen is converted into porphyrin and other pigments, whereas in alkaline solution the porphobilinogen is destroyed without formation of pigment. This lability together with the lack of solubility in organic solvents renders the preparation of pure porphobilinogen a matter of considerable difficulty. In an attempt to obtain a stable material suitable for investigation, some of the porphobilinogen solution (adjusted to p_H 6.6 with sodium hydroxide and therefore containing sodium acetate) was dried cryoscopically by Dr. Elford at the National Institute for Medical Research. The light, white sodium acetate powder thus obtained contained 70 per cent of the porphobilinogen of the original solution. The porphobilinogen adsorbed on the sodium acetate could not be eluted with ether, petroleum ether, acetone or ethyl acetate. Traces could be eluted with isobutyl alcohol, amyl alcohol and ethyl alcohol, but the extent of elution of traces appeared to parallel the solubility of sodium acetate in the solvent. Thus, no effective purification of the chromogen resulted. The cryoscopically dried sodium acetate still showed a positive reaction for porphobilinogen two years after its preparation. No method of preparing the pure material from it has been devised at the time of this report.

Histologic Appearance of the Central Nervous System.—The detailed histologic examination of the central nervous system has not yet been completed but will ultimately be reported fully elsewhere. In the meantime, Dr. A. Meyer has given me the following provisional report:

"The only established lesion in this case was a retrograde degeneration of nerve cells in the anterior horn in all segments, particularly marked in the posterolateral group of the cervical segments. In some of the thoracic segments the retrograde

degeneration was particularly severe in the intermediolateral cell column, which is supposed to serve visceral function. This retrograde degeneration was probably the result of the peripheral neuritis. The significance of the degeneration of the visceral column of the thoracic segments was not clear to me. Apart from these the central nervous system did not show any definite pathologic changes. The peripheral nerves were not available for investigation."

A section of the thoracic region of the spinal cord was examined microscopically in ultraviolet rays for the presence of the orange, fluorescent granules which, according to Klüver (1944),[8] are present in the central nervous system of the higher animals, including man. A few such granules were found with difficulty in striking contrast to the ease with which large numbers were found in a section of the corresponding region of the normal spinal cord of a person of an age similar to that of the patient. Fixation was identical in both.

COMMENT

The present case is of particular interest in that, whereas the clinical features were typical of classic acute porphyria, the urine contained small amounts of preformed porphyrins but relatively enormous amounts of porphobilinogen. In those cases described by Waldenström and Vahlquist[9] and in that described by Prunty,[4] the daily excretion of this chromogen was of the order of a few hundred units per day, whereas in the present case a daily excretion of between 10,000 and 25,000 units occurred over a period of several weeks. As a result of the almost complete absence of preformed porphyrins in urine of normal color, the true diagnosis remained obscure for a month before a chance observation by a ward sister led to the special examination for pigments. Even then, since the specimen sent to the laboratory was fresh and quite normal in color, the condition would not have been suspected but for the strong positive Ehrlich reaction associated with a negative reaction in the Schlesinger test with zinc acetate.

The absence of significant amounts of porphyrins in the serum and of any gross amounts of preformed porphyrins in the urine renders it possible that it is the colorless precursor, porphobilinogen, which is the agent responsible for the manifestation of the disease. Against this possibility is the undisputed fact that porphyrins are photosensitizing agents and can cause spasm of surviving gut in vitro but further research on the physiologic properties of the chromogen is highly desirable.

In classic acute porphyria both abdominal symptoms and disturbances of the central nervous system are present, but some cases have been described in which one or the other of these features has been much the more prominent. Nevertheless, it has never been possible to correlate the variability in the clinical picture with any definite pattern

8. Klüver, H.: On Naturally Occurring Porphyrins in the Central Nervous System, Science **99**:482, 1944.

9. Waldenström, J., and Vahlquist, B.: Studies on Excretion of Porphobilinogen in Patients with So-Called Acute Porphyria, Acta med. Scandinav. **117**:1, 1944.

of excretion of porphyrins. Since Waldenström (1934) [10] isolated a porphyrin of a melting point of 264 C., claimed by him to be uroporphyrin III, it has been tacitly assumed that, whereas in congenital porphyria the major ether-insoluble porphyrin is uroporphyrin I, in acute porphyria the major ether-insoluble porphyrin is this Waldenström porphyrin. Small amounts of uroporphyrin I have on occasion been isolated with larger quantities of the Waldenström porphyrin (Mertens,[11] 1937), a finding which has been confirmed in 2 cases of acute porphyria observed by the present author. However, the resolution by the chromatographic technic of Grinstein, Schwartz and Watson (1945)[6] of some preparations of the Waldenström porphyrin into uroporphyrin I and another porphyrin (probably heptacarboxylic in nature) necessitates revision of the ideas on the subject. Moreover, the demonstration by Watson, Schwartz and Hawkinson (1945),[12] with confirmation by Prunty (1946) [4] as well as in the present case, that those preparations of the Waldenström porphyrin not so resolvable into two porphyrins yield on decarboxylation coproporphyrin I amongst other products, makes it clear that the earlier concepts of the relation between the type of porphyrin excreted and the clinical type of porphyria were premature. Watson and his associates suggested that these other porphyrins may, with the addition of uroporphyrin I, form products which may or may not be resolvable by the chromatographic technic into their components. One thus has to consider the possibility that excretion of uroporphyrin I occurs in all cases of porphyria, whether of congenital or acute form, and that the significant feature of acute porphyria may be the presence of the other incompletely characterized porphyrins. Further studies of these porphyrins will be essential before the present confusion can be cleared up.

The relative proportions of coproporphyrin I and III excreted in the urine are also extremely variable and bear no relation to the classic manifestations of the disease. In some cases coproporphyrin III predominates; in others, coproporphyrin I. It is possible that this variability may be related to the skill of the worker in isolating small quantities of coproporphyrin III; the new method of estimating the

10. Waldenström, J.: Some Observations on Acute Porphyria and Other Diseases with a Change in the Excretions of Porphyrins, Acta. med. Scandinav. **83**:281, 1934.

11. Mertens, E.: Ueber die bei akuter Porphyrie auftretenden Porphyrine, Ztschr. f. physiol. Chem. **250**:57, 1937.

12. Watson, C. J.; Schwartz, S., and Hawkinson, V. E.: Studies of the Uroporphyrins: II. Further Studies of the Prophyrins of the Urine, Feces, Bile and Liver in Cases of Porphyria, with Particular Reference to a Waldenström Type Porphyrin Behaving as an Entity on the Tswett Column, J. Biol. Chem. **157**:345, 1945.

proportions of the isomers (Schwartz and others,[13] 1947), depending on the differential extinction of fluorescence by acetone, is likely to prove a valuable weapon in the investigation of new cases of the disease. The amounts of porphyrin excreted daily vary greatly from case to case. I have examined the urine in a case with clinical features almost identical with those of the present one, yet in which the uroporphyrin excretion amounted to only a fraction of a milligram per day. It seems impossible in the light of present knowledge to assess the significance of the variation.

In the present case the amount of cytochrome and myoglobin in the muscles and that of catalase in the liver was not below normal, nor was there any evidence of increased hemolysis. It therefore seems unlikely, though not impossible, that the excreted porphyrins are derived from these sources. If this were the case, unless there were complete breakdown and resynthesis of the porphyrin structure the excreted porphyrins should be of series III rather than of series I. Although stercobilin was not isolated, the pigment was present in quantity in the feces and it is unlikely that there was any major alteration of catabolism of biliary pigment.

It is pointless to comment more than briefly on the possible significance of the apparent diminution of the orange, fluorescent granules in the spinal cord. The isolated observation recorded here can mean little without further confirmation. Such a diminution of fluorescent material, if confirmed, could represent a change secondary to the degeneration of the central nervous system. The central nervous system is unlikely to be the main source of the large amounts of excreted porphyrins unless there is an extraordinarily rapid turnover of these pigments in that site. Kluyver (1944)[8] produced evidence suggesting that the granules contained coproporphyrin and/or protoporphyrin but was unable to identify the isomer type. It is possible that part or all of the excess urinary coproporphyrin in cases of acute porphyria could be derived from the central nervous system, a possibility supported by the recent observation of Watson (1947) [14] that increased excretion of coproporphyrin in the urine occurs in anterior poliomyelitis.

SUMMARY

This paper presents the clinical, pathologic and biochemical features of a typical case of acute porphyria characterized by the excretion of large amounts of porphobilinogen in the urine, together with relatively

13. Schwartz, S.; Hawkinson, V. E.; Cohen, S., and Watson, C. J.: A Micromethod for the Quantitative Determination of the Urinary Coproporphyrin Isomers, (I and III), J. Biol. Chem. **168**:133, 1947.

14. Watson, C. J.: The Urinary Coproporphyrins in Health and Disease, Physiol. Rev. **27**:478, 1947.

small amounts of preformed porphyrins. The urinary coproporphyrin appeared to be mainly type I. After acidification of the urine the color, previously normal, became brown-red; an ether-insoluble porphyrin could then be isolated, possessing all the properties of that porphyrin described by Waldenström. On decarboxylation of this ether-insoluble porphyrin coproporphyrin I was obtained, in addition to other products, so the specimen of the Waldenström porphyrin could have not been uroporphyrin III.

Dr. Philip Ellman was responsible for the clinical care of the patient. Miss J. Whidborne gave technical assistance at an early stage of the biochemical investigations, and Mr. J. Smiles, with the ultraviolet microscopic examination of the spinal cord. Dr. Hartree estimated the cytochrome, myoglobin and catalase levels, and Dr. Elford performed the cryoscopic drying of the porphobilinogen solution. Apparatus used was purchased with grants from the Central Research Fund of the University of London and from the Medical Research Council.

HYPERTHYROIDISM

Treatment with Radioactive Iodine

SERGEI FEITELBERG, M.D.
PAUL S. KAUNITZ, M.D.
SOLOMON SILVER, M.D.
NORMAN SIMON, M.D.
LOUIS R. WASSERMAN, M.D.
AND
STEPHEN BENNETT YOHALEM, M.D.
NEW YORK

THE THYROID gland has the ability to concentrate the isotopes of iodine, and this selective uptake is increased greatly in hyperplastic disease of the thyroid gland. Since the initial investigations by Hertz, Roberts and Evans,[1] Hamilton and Soley[2] and Hertz and others[3] there have been numerous reports on the use of radioactive iodine (I^{130} and I^{131}) in the treatment of patients with hyperthyroidism. The various investigators differ somewhat concerning dosage and the management of their patients, but the basic approach is the same. An initial calculated dose of radioactive iodine is administered orally to the patient, and the majority of investigators prescribe additional therapy as indicated by the subsequent course. Since we studied over 200 patients in the two and a half years previous to this report, we believe it worth while to record our experience.

MATERIAL

The data were sufficiently complete to justify conclusions in 184 cases. The patients were followed from three to thirty months; all those followed for the minimum period were included. There were 146

The radioactive iodine (I^{131}) was supplied on allocation by the United States Atomic Energy Commission.

From the Physics Department and the Medical Services, Mount Sinai Hospital. Dr. Kaunitx is Sara Welt Fellow; Dr. Simon is Dazian Fellow, and Dr. Yohalem is Elsa and William Menke Fellow.

1. Hertz, S.; Roberts, A., and Evans, R. D.: Proc. Soc. Exper. Biol. & Med. **38**:510, 1938.

2. Hamilton, J. G., and Soley, M.: Am. J. Physiol. **127**:557, 1939.

3. Hertz, S.; Roberts, A.; Means, J. H., and Evans, R. D.: Am. J. Physiol. **128**:565, 1940.

females and 38 males in the group. The age distribution is noted in table 1.

Of these patients with hyperthyroidism, 150 had diffuse toxic goiter, 4 had substernal goiter and 28 had adenomas; in 2 patients with clinical hyperthyroidism the gland could not be palpated. The distribution of the type of pathologic change was weighted by our reluctance, which will be discussed later, to treat adenomatous glands except in those patients in whom the lesions were rendered inoperable by the presence of cardiac or other disease. In all patients the diagnosis was suspected clinically and corroborated uniformly by determinations of the basal metabolic rate and by excretion tests with radioactive iodine; determinations of

TABLE 1.—*Distribution of Patients by Age Group*

Age, Decades	Patients
3	19
4	34
5	44
6	45
7	30
8	12
Total	184

TABLE 2.—*Previous Therapy*

Type	Instances
None	110
Administration of thiouracil or its derivatives (exclusive of preoperative use)	52
Surgical intervention (1 or more operations)	24
Radiotherapy	6
Administration of iodine compounds (exclusive of preoperative use)	27
Total	219

cholesterol and serum iodine were made for the majority. The first patients treated by us with radioactive iodine had conditions which were the result of failure of other forms of therapy, including surgical intervention and the administration of antithyroid drugs; the impressive results increased our confidence, and at the time of this report all patients in Mount Sinai Hospital with diffuse toxic disease of the thyroid gland are treated with I^{131}. The basal metabolic rate prior to treatment in the present series varied from plus 6 per cent to plus 101 per cent, with a distribution as shown in the figure. The average pulse rate was 120 beats per minute; 18 patients had atrial fibrillation. In table 2, the previous therapy of all patients is listed (the total is in excess of the number of patients because of the multiplicity of previous attempts at cure). In each of 3 patients, three operations, radium therapy and administration of thiouracil had been tried prior to our treatment.

The radioactive iodine (I^{131}) was that supplied as potassium iodide by the Atomic Energy Commission. No significant amount of carrier iodine was used. The iodine was standardized on the basis of the "New York" millicurie.[4] This millicurie is roughly equivalent to 0.67 Oak Ridge millicuries. There is some evidence that the New York millicurie is equal to 43 million disintegrations per second, or to 1.17 "correct" millicuries. Doses are expressed in terms of the New York millicurie.

METHOD

The size of the thyroid gland was estimated by three observers, and an initial dose, based on this estimate and on the measured excretion of a tracer dose, was administered in an attempt to deliver approximately 10,000 roentgen equivalents to the gland. The average quantity of I^{131} used in these 184 patients was 8.2 millicuries, with a maximum initial dose of 11 millicuries and a minimum effective dose (after operation) of 1.7 millicuries. The average dose was about 10,000 roentgen equivalents, or about 80 microcuries taken up per gram of thyroid gland. Our technic of dosage is similar to that of Hertz and Roberts [5] and Chapman and Evans [6] but differs from that of Werner and his associates [7] and others who use a standard initial dose with repeated therapy as needed. The administration of strong iodine solution (Lugol's) after radioactive iodine, as reported by Hertz and Roberts, was not carried out routinely in these cases since it was our feeling that the radioactive iodine was adequately fixed in the gland without the addition of stable iodine. In 7 cases of extremely severe disease we administered this solution from the third to the eighteenth day after radioisotope treatment in order to accelerate a remission in symptoms. Administration of the drug was then discontinued so that the effect could be evaluated after six to eight weeks, probably as a measure of the effect of radiation alone. We attempted to use a single effective therapeutic dose because we feel that the calculated risk of an increased number of patients with hypothyroidism is less than the risk of prolonged treatment with smaller doses in patients with so serious a disease as hyperthyroidism. We

4. Feitelberg, S.: Science **109**:456, 1949.

5. Hertz, S., and Roberts, A.: Radioactive Iodine in Study of Thyroid Physiology: Use of Radioactive Iodine Therapy in Hyperthyroidism, J. A. M. A. **131**:81 (May 11) 1946.

6. Chapman, E. M., and Evans, R. D.: Treatment of Hyperthyroidism with Radioactive Iodine, J. A. M. A. **131**:86 (May 11) 1946.

7. Werner, S. C.; Quimby, E. H., and Schmidt, C.: Bull. New York Acad. Med. **24**:549, 1948.

followed this approach even in treating patients with mild symptoms because of the frequency of unpredictable exacerbations in the course of the disease.

RESULTS

In the average patient, subjective improvement was noted in two to four weeks, usually in the third week after treatment, and objective improvement, in four to eight weeks. Patients who were not well by clinical and laboratory criteria in eight weeks received a second dose of radioactive iodine; as noted later, a few required a third dose.

Improvement was not uniform in all instances. In about 20 per cent of the patients fall of the metabolic rate and clinical improvement were optimal at eight weeks but slight relapses were noted in the ensuing four weeks. It is for this reason that data on patients followed for the shorter period of time are not included in this report. Occasionally a period of hypothyroidism occurred which subsided without treatment. One hundred and thirty-two patients were cured with a single dose of I^{131}, 43 required a second treatment and 9 had three treatments. Two patients in the last category required the third treatment five and eleven months respectively after an apparent remission. The distribution of the basal metabolic rates determined after treatment may be seen in the figure. The average pulse rate, which was 120 prior to treatment, was 75 after treatment. Only 6 of the patients had atrial fibrillation after treatment, as compared to 18 before treatment. The return to normal sinus rhythm after treatment with I^{131} occurred spontaneously in 10 of the 12 patients in whom remissions occurred and followed the exhibition of quinidine in 2. In the remaining patients quinidine was not administered because of coexistent rheumatic heart disease with fibrillation of many years' duration. The average weight gain, excluding those patients in whom hypothyroidism developed, was 14.6 pounds (6.7 Kg.).

Radiation sickness, described by others as occuring after the administration of these relatively small doses of I^{131}, was not observed, nor was there any effect on the peripheral blood. In only 4 patients was there tenderness or swelling of the thyroid gland after therapy. This complication was noted particularly by Chapman, Skanse and Evans,[8] largely in patients treated with I^{130}, with which the radiation effect is more acute. Soley and Miller[9] likewise reported the complication, as well as temporary exacerbation of the disease. This difficulty was not observed in our series except possibly in 1 fatal case, discussed later.

8. Chapman, E. M.; Skanse, B. M., and Evans, R. D.: Radiology **51**:558, 1948.

9. Soley, M., and Miller, E. R.: M. Clin. North America **32**:3, 1948.

Neither post-therapeutic exophthalmos nor increase of exophthalmos occurred in any of our patients. However, in 2 of 3 patients with progressive exophthalmos prior to therapy the condition continued after treatment; in the third patient it was apparently arrested. Shrinkage of the gland was observed in 121 of our patients, in some to an extreme degree, with disappearance of palpable goiters estimated to weigh 150 to 200 Gm.

In 13 patients hypothyroidism developed after treatment and had lasted from five to twenty-one months at the time of this report. In all instances this was readily controlled with desiccated thyroid in daily doses of 15 to 200 mg. In table 3 the essential data on these patients is presented.

TABLE 3.—*Data on 13 Patients with Post-Therapeutic Hypothyroidism*

Patient	Age, Years	Sex	Previous Therapy*	Dose of I^{131} Millicuries	Comment
1	41	F	S T I	12	Overdose in extremely toxic patient after operation
2	27	F	O	2, 2, 4	Unwise increase in third dose
3	46	F	S T	8	Overdose in toxic patient after operation
4	53	F	O	6	
5	40	F	O	8	
6	50	M	T	9	
7	46	F	O	5, 6, 8	Extremely toxic patient; gland never palpable
8	61	F	O	8	
9	29	F	O	10	
10	32	M	T	3, 4	
11	48	F	O	4	
12	54	F	O	8	
13	41	F	S S S T R I	2	Extreme toxicity; 3 operations; gland not palpable

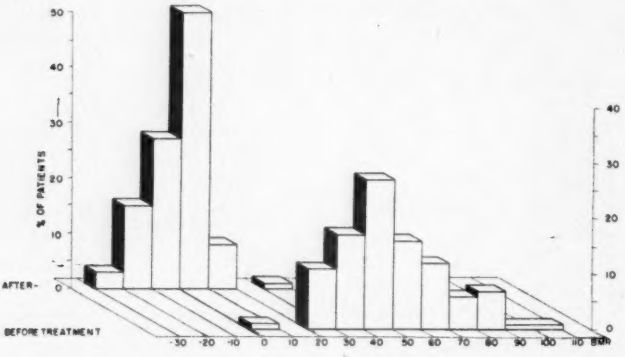
* S indicates operation; T, administration of thiouracil derivatives; I, administration of strong iodine solution; O, no therapy, and R, external radiation.

Cases 1, 3 and 13 demonstrate the necessity for special caution in cases of postoperative relapse. In 2 of these we probably made an error in estimating the weight of the gland including the palpable scar tissue. The third patient (no. 13) had a six year history of repeated failure of various forms of therapy and maintained a basal metabolic rate of plus 68 per cent. Despite very cautious dosage, true myxedema (the basal metabolic rate was minus 38 per cent) developed in the fourth month after treatment and continued for twenty-one months to the time of this report. Cases 2, 7 and perhaps 10 illustrate the danger of increasing the original dose in the absence of a prompt therapeutic effect. Our experience indicates that a second dose should always be less than the first, probably because, with our methods, the first dose is an attempt to deliver a full therapeutic effect. The 13 patients in whom post-treatment hypothyroidism developed were completely comfortable on

thyroid therapy, and their general status, as exemplified in case 13 (table 3), represented a very marked improvement.

The percentage of hypothyroid sequelae (7 per cent) was comparable to that reported by other workers, including those who use a standard initial dose smaller than our average dose. In about half the cases the source of error in calculating the therapeutic dose was apparent; it is hoped that post-treatment hypothyroidism can largely be eliminated in the future.

Four patients who were treated have since died (of coronary thrombosis, rheumatic heart disease, stroke, and in an automobile accident), but in each the disease had been well controlled. Data on these 4 patients are included with those of 163 others, in whom excellent



Basal metabolic rate in 184 patients.

therapeutic results were achieved; we therefore report 167 cured patients in excellent condition without complication. Two other patients were cured of hyperthyroidism but continued to have the progressive exophthalmos which they had before treatment; these results are thought to be fair. The cure of 182 of 184 hyperthyroid patients and the absence of any post-therapeutic sequelae in 167 of the 184 is a higher rate of cure than has been reported previously. However, this represents a terminologic rather than a real difference, since other authors have listed cases as failures in which they failed to achieve a cure after a single dose. That is as illogical as listing the first stage of a two stage operation as a therapeutic failure.

We had 2 absolute failures in our series. In the first case a patient with a gland estimated to weigh 140 Gm. was treated early in our experience with 8 millicuries of I^{131}. She was seen three months later

and told to return for further treatment but left our clinic for care elsewhere. Six months later, without further therapy, she died of thyroid storm as a complication of lobar pneumonia in the fifth month of pregnancy. The second patient, who was extremely obese and toxic, with a 200 Gm. gland, received 10 millicuries of I^{131}. On the following day she died of hyperpyrexia, probably in thyroid storm. This is the only case which we regard as a therapeutic fatality.

The initial dose employed in this series failed to give a uniform result. This variation in response was probably due to several factors, among which were the following: (1) errors in estimating the weight of the gland; (2) variations in biologic half-life, which was assumed to be six days; (3) nonuniform distribution of I^{131} within the gland, and (4) variable sensitivity of the gland to the radiation. With respect to the second point, it should be recalled that a biologic half-life as short as three days has been reported for I^{131}; in such an instance the actual dose would be only half the calculated dose. The maximum theoretic error in underestimating the dose is 30 per cent. In our experience the estimation of the weight of the gland has been a better guide to therapy than the apparent toxicity of the patient or the level of the basal metabolic rate.

RESTRICTIONS

At the onset of this program treatment was restricted to patients over the age of 45, with few exceptions. There is little theoretic and no historical basis for a fear that this brief radiation treatment of the thyroid gland will induce malignant disease. We therefore no longer observe any age limit in our selection of patients. In the case of toxic adenoma the problem is somewhat different. Solitary adenomas of the thyroid gland are potentially malignant, although there is wide difference of opinion as to the frequency of this development. We feel that at present all such patients should be treated surgically, not because of the fear of inducing cancer, but for fear of missing it.

CONCLUSION

Because of the simplicity of the method, the absence of important complications and the excellence of the results it is our opinion that use of internal radiation with I^{131} is the treatment of choice in diffuse toxic goiter. In toxic adenoma its use should be reserved for those patients to whom surgical intervention is not applicable because of coincident disease which would inordinately increase the operative risk.

SUMMARY

1. Results are reported in the treatment with radioactive iodine (I^{131}) of 184 patients with hyperthyroidism.

2. One hundred and eighty-two patients were cured of hyperthyroidism. Of these, post-therapeutic hypothyroidism developed in 13. Two of 3 patients with progressive exophthalmos before treatment continued to show progressive exophthalmos.

3. We consider use of internal radiation with I^{131} the treatment of choice for patients with diffuse toxic goiter.

ADDENDUM

Since this article was submitted for publication, we have treated an additional 106 patients, all of whom were cured. Myxedema developed in 5. One patient required seven treatments with I^{131} (total dose, 38 microcuries).

HYPERMETABOLIC STATES WITHOUT HYPERTHYROIDISM (NONTHYROGENOUS HYPERMETABOLISM)

SOLOMON SILVER, M.D.

PHILIP POROTO, B.S.

AND

EDWARD B. CROHN, M.D.

NEW YORK

IN THE closing years of the past century, primarily as a result of the studies by Adolf Magnus-Levy, it became general knowledge that the commonest cause of a consistently elevated basal metabolic rate is hyperthyroidism. It was not long thereafter that clinicians began to note that there were isolated instances of significant elevations of the basal metabolic rate that could not be explained on the basis of thyroid hyperfunction. Although not a few references can be found to this apparently anomalous situation,[1] no comprehensive study of the phenomenon has been undertaken so far as we can ascertain. It is the purpose of this communication to present data concerning a considerable group of these patients with particular respect to the level of thyroid function.

It is generally accepted that, among others, the following conditions are frequently associated with an elevated basal metabolic rate: (1) disorders of the blood-forming organs: severe anemia, polycythemia, leukemias, multiple myeloma, Hodgkin's disease, lymphosarcoma; (2) cardiac disorders: congestive heart failure, some cases of hypertension, arteriovenous aneurysm; (3) malignant tumors, with or without metastases; (4) pheochromocytoma; (5) extensive skin diseases with erythroderma, and (6) Paget's disease of bone. This list does not complete the series, but it does include the commonest conditions encountered clinically in which an elevated basal metabolic rate is not uncommon.

From the Medical Service and the laboratories of the Mount Sinai Hospital.

1. Minot, G. R., and Means, J. H.: The Metabolism-Pulse Ratio in Exophthalmic Goitre and in Leukemia, with Remarks on Certain Similarities in the Symptomatology of These Diseases, Arch. Int. Med. **33**:576 (May) 1924. Hamburger, W. W., and Lev, M. W.: Basal Metabolism in Organic Heart Disease with Decompensation: Preliminary Report, J. A. M. A. **84**:587 (Feb. 21) 1925. Boas, E. P., and Shapiro, S.: Further Observations on Patients with Hypertension and Increased Basal Metabolic Rate, Am. Heart J. **1**:643, 1926.

We have attempted to evaluate the functional state of the thyroid gland in patients with disorders of this group by applying two of the more modern methods of studying thyroid function: the determination of the level of the protein-bound iodine in the plasma and observations following administration of tracer doses of I^{131}, a radioactive isotope of iodine.

METHODS

1. *Selection of Cases.*—Careful determinations of the basal metabolic rate were carried out on a large series of patients admitted to the wards of the hospital with the disorders previously mentioned. Those with normal rates were discarded from this series. The further studies were carried out on all the patients whose basal metabolic rates were elevated.

2. *Determination of the Basal Metabolic Rate.*—The basal metabolic rate was determined with the usual precautions, with use of a closed circuit type of apparatus with a soda lime absorber. The patients were hospitalized and studied in the morning in the postabsorptive state. The results were expressed in the usual manner. As some of these disorders are occasionally accompanied with fever, the determinations were always made when the patients were in an afebrile period. Duplicate readings were always obtained.

3. *Determinations of Protein-Bound Blood Iodine.*—With use of methods previously described from this laboratory,[2] the level of the protein-bound or nondialyzable iodine of the plasma was determined in each case. Briefly stated, the method is as follows: Five cubic centimeters of oxalated plasma is digested in a mixture of concentrated (eighteen times normal) sulfuric acid with an excess of potassium permanganate. The cooled digest is transferred to a distilling apparatus and reduced with phosphorous acid in excess. The mixture is distilled and the distillate trapped in an alkali solution which now contains all the iodine as iodide. This is evaporated to small volume, oxidized with potassium permanganate and acidified and the excess permanganate removed with sodium nitrite. The excess nitrite is removed with urea and iodide added to liberate free iodine. Soluble starch is used as an indicator, and the titration is performed with 0.002 normal sodium thiosulfate delivered from a microburet. Duplicate determinations were always performed and repeated if checks were not obtained. The upper limit of normal by our method is 8 micrograms per hundred milliliters of plasma, with most normal values falling between 5 and 7 micrograms.

4. *Radioactive Iodine Excretion Studies.*—One hundred microcuries of I^{131} as potassium iodide was administered orally in aqueous solution, and the amount excreted in the next twenty-four hour urine sample was determined. As the previous administration of iodine, thiourea compounds or thyroid extract can invalidate the significance of this procedure, care was taken to exclude any of these factors. It is generally accepted that patients with active hyperthyroidism usually excrete less than 20 per cent of the ingested dose.

RESULTS

The results are presented in the table.

2. Silver, S.: The Nature of the Blood Iodine, J. Mt. Sinai Hosp. **7**:97, 1940; The Nature of the Blood Iodine and Its Determination, J. Lab. & Clin. Med. **28**:329, 1942.

COMMENT

The cause of the increased oxygen consumption in a patient with toxic diffuse goiter is now generally accepted to be a hyperfunctioning of the thyroid gland with an increased secretion of its hormone. Briefly stated, the evidences for this increased activity of the thyroid gland are the histologic evidences of active hyperplasia, the consistent elevation of the "hormone" or protein-bound iodine of the plasma, the increased avidity for iodine and the increased turnover rate of iodine as measured by studies with radioactive iodine tracers. The calorigenic action of the thyroid hormone offers an immediate, and probably correct, explanation for the hypermetabolism.

In the group of patients studied, the situation is not so clear. Studies of the thyroid glands of patients with these disorders do not reveal

Relation of Plasma Iodine Level, Basal Metabolic Rate and Excretion of Radioactive Iodine

Disease	No. of Cases	Plasma Iodine Concentration, Megm./100 Cc.		Elevation of Basal Metabolic Rate, %		I^{131} Excretion, %	
		Range	Average	Range	Average	Range	Average
Leukemia, myeloid and lymphatic	16	6.4- 9.0	7.1	12-91	46	40-50	46
Multiple myeloma	11	2.5- 9.7	6.7	14-60	28	23-60	43
Lymphoma, including Hodgkin's, lymphosarcoma, lymphoblastoma, reticulum cell sarcoma, etc.	14	5.5-10.0	7.0	11-65	38	31-68	47
Carcinoma, localized and metastatic	23	5.6- 9.8	7.0	6-57	29	26-55	39
Hypertension	17	5.7- 8.2	6.9	12-75	40	27-55	43
Congestive heart failure	4	6.6- 7.0	6.8	20-32	27	26-56	43
Paget's disease of bone, polycythemia, Cushing's syndrome	4	6.0- 8.4	6.9	16-38	24	40-61	51

evidences of hyperplasia, with the possible exception of patients with pheochromocytoma, in whom thyroid hyperplasia has been described and is probably a result of epinephrine stimulation.

It is not essential, or even likely, that there is a single explanation for the hypermetabolism in our group of patients without hyperthyroidism. For some of them fairly obvious explanations offer themselves. For example, one is tempted to explain the increased basal metabolic rate in a patient with congestive heart failure by the dyspnea and the increased muscular work that it engenders. In a patient with erythroderma there is an obvious increase in heat loss from the body as a result of the large volume of blood flowing through the skin, and increased heat production can be visualized as a homeostatic mechanism to maintain the normal body temperature. The increased cardiac output in patients with arteriovenous aneurysm and with Paget's disease of bone may cause an increase in oxygen requirements sufficient to elevate the basal metabolic rate significantly. In patients with various neoplasms and

diseases of the blood-forming organs, the actual metabolic requirements of the large masses of active cells may be an adequate explanation for the recorded observations. In a patient with a tumor one must also consider the possibility of the accumulation of degradation products such as amino acids and polypeptides, which are known calorigenic agents. We can offer no obvious explanation for the increased oxygen consumption in some patients with hypertensive vascular disease without heart failure. Increased cardiac work cannot explain the findings, particularly when many patients with the same blood pressure readings show a normal basal metabolic rate. Whether the stimulus to increased metabolism originates in unknown diencephalic centers remains a matter of conjecture.

SUMMARY AND CONCLUSIONS

We have presented observations on a series of 89 patients with various diseases known to produce an increase of the basal metabolic rate without the clinical picture of toxic diffuse goiter.

Studies of thyroid function by means of determinations of blood levels of protein-bound iodine and by the use of excretion studies employing tracer doses of I^{131} have demonstrated that there is no evidence of increased thyroid activity in these disorders.

The mechanism of the hypermetabolism in these patients is not clear, but it is on a different basis from that found in toxic diffuse goiter.

PULMONARY NODULES ASSOCIATED WITH MITRAL STENOSIS

STANLEY H. SAHN, M.D.
AND
IDA LEVINE, M.D.
BROOKLYN

THE LUNG parenchyma in patients with compensated mitral stenosis has usually been reported as free of pathologic signs. Physicians have been taught to expect a normal lung picture in the early stages of this disease. With time, the progressive fibrosis of the valve and the chordae tendineae bring about cardiac inefficiency with diffuse engorgement of the pulmonary vessels, best seen at the hilus. This progressive loss of cardiac reserve finally manifests itself as outright decompensation, with pulmonary edema and pleural effusions. Except for the intercurrent complication of infarcts, this is the routine description of the pulmonary findings.[1]

However, in the more recent roentgenologic texts and in the literature, there have occasionally been described disseminated miliary nodules in the lungs of patients with long-standing mitral stenosis.[2] This occurrence has been considered unusual; less than 25 cases were reported in the American literature during the ten years previous to this report. Those cases which were reported were subdivided on the basis of the radiopacity of the nodules; they were grouped in the "soft"-appearing or the "calcific"-appearing densities. The very fine, soft, miliary stippling, so often confused with miliary tuberculosis, pneumoconiosis, sarcoidosis, miliary bronchopneumonia, etc., may be seen in about 1 per cent of the patients with mitral stenosis, according to Scott and his associates.[3] They reviewed a series of 200 roentgenograms of the chest. The calcified or ossified miliary or submiliary opaque areas have been confused with tuberculous lesions, histoplasmosis infections, and other conditions; no statistical evaluation of their incidence has been found.

From the Chest Diseases Service of Dr. Harry B. Reibstein, Beth-El Hospital.

1. Cecil, R. L.; McDermott, W., and Wolff, H. G.: A Textbook of Medicine, ed. 7, Philadelphia, W. B. Saunders Company, 1947, pp. 367-368.

2. Rigler, L. G.: The Chest: A Handbook of Roentgen Diagnosis, Chicago, The Year Book Publishers, Inc., 1946, pp. 78-79. Schwedel, J. B.: Clinical Roentgenology of the Heart, Annals of Roentgenology Series, 18, New York, Paul B. Hoeber, Inc., 1946, p. 257.

3. Scott, L.; Park, S., and Lendrum, A.: Clinical, Radiological and Pathological Aspects of Pulmonary Hemosiderosis, Brit. J. Radiol. **20**:100-108, 1947.

Probably because of the divergence of interest and purpose in the reporting of these cases by radiologists, phthisiologists, pathologists, cardiologists, and others, there has been no final or unanimous clarification of the pathogenesis of these areas of density or of the mechanism responsible for their varying radiopacity. No single author has had enough histologic material to warrant his making a conclusive statement as to the physiopathologic factors. Recently Pendergrass and his co-workers [4] were able to report 4 autopsies in addition to their clinical material. They attributed the "calcific" areas to a combination of brown induration, pulmonary hyperemia and pulmonary congestion. The "soft" areas were explained on the basis of endogenously derived deposits of iron pigment; yet, of the 4 patients whom they reported as having pulmonary hemosiderosis, 2 showed microscopic evidence of calcification in addition to the aggregates of hemosiderin. We therefore suggest that the separation of noncalcific and calcific types of stippling is an unnecessary one. We believe that both have a similar physiopathologic basis. Patients with either type exhibit a prolonged history of mild attacks of failure and a microscopic picture of iron deposits, as well as the small localized fibrotic areas, the alveoli filled with heart failure cells, the dilated blood vessels, etc., which have been described in the literature.[5] The patients with calcification or ossification simply react to the tissue degeneration in a more extreme fashion.[6]

If one accepts these histopathologic factors, it becomes difficult to explain why these areas of nodular density are reported so infrequently. One may, of course, entertain certain possibilities. Many patients do not seek medical care during their relatively asymptomatic years. With the appearance of gross decompensation, the fine areas of density may be masked by the edema; after the edema clears, the need for a comparative film is minimized and again an opportunity is lost. It would seem plausible to expect an incidence greater than the reported 1 per cent if these patients were studied roentgenologically at intervals throughout the entire course of the illness;[7] but, regardless of the exact reasons for

4. Pendergrass, E. P.; Lame, E. L., and Ostrum, H. W.: Hemosiderosis of the Lung Due to Mitral Disease, Am. J. Roentgenol. **61**:443-456, 1949.

5. Neubuerger, K. T.; Geever, E. F., and Rutledge, E. K.: Rheumatic Pneumonia, Arch. Path. **37**:1-15 (Jan.) 1944. Fishberg, A. M.: Heart Failure, Philadelphia, Lea & Febiger, 1937, pp. 199-218.

6. Elkeles, A., and Glynn, L. E.: Disseminated Parenchymatous Ossification in the Lungs in Association with Mitral Stenosis, J. Path. & Bact. **58**:517-522, 1946. Delafield, F., and Prudden, T. M.: A Text-Book of Pathology, ed. 16, revised by F. C. Wood, Baltimore, William Wood & Company, 1936, pp. 64-67.

7. Hurst, A.; Bassin, S., and Levine, I.: Miliary Densities Associated with Mitral Stenosis, Am. Rev. Tuberc. **49**:276-285, 1944.

it, the infrequency of this finding has led to another problem, that is, to the failure to consider mitral stenosis as a possibility in the differential diagnosis of pulmonary lesions. This failure is particularly important at this time, in view of the growing interest in the correlation of pulmonary calcification and sensitivity to histoplasmin.

Until recently every pulmonary area of calcification was automatically labeled as tuberculous in origin. So widespread was this attitude of "diagnosis by probability" that whenever a negative reaction to the tuberculin test was found in a patient with such a lesion the occurrence was explained away as being due either to complete eradication of viable bacilli or to individual anergy.[8] Other etiologic possibilities were considered too remote to require investigation. The past decade saw a change in this type of reasoning. It was learned that coccidioidomycosis may cause pulmonary calcification,[9] and, even more significant, that histoplasmosis also may cause calcification.[10] It was found that whereas 1 of 3 persons showing a positive reaction to the histoplasmin test shows calcification on roentgenologic studies of the chest, only 1 of 10 who show a positive reaction to the tuberculin test has calcification. Moreover, although the incidence of persons showing a positive reaction to the histoplasmin test is considerable (ranging from 10 to over 68 per cent of the population, depending on the geographic area studied), the incidence of persons showing a positive reaction to the tuberculin test has been dropping steadily (it has become 8 per cent in Minneapolis).[11] There is now agreement that pulmonary calcification should no longer be interpreted as tuberculous in every instance. Instead, it should be attributed to either tuberculosis or histoplasmosis in the majority of cases. Since 68 per cent to 99 per cent of the patients with calcification studied showed a positive reaction to the tuberculin test, a positive reaction to the histoplasmin test or both, the word "majority" must be included for the sake of accuracy.[12]

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8. Crimm, P. D., and Short, D. M.: Tuberculin Anergy in Cases with Pulmonary Calcifications, Am. Rev. Tuberc. **39**:64-69, 1939.

9. Aronson, J. D.; Saylor, R. M., and Parr, E. I.: Relationship of Coccidioidomycosis to Calcified Pulmonary Nodules, Arch. Path. **34**:31-48, 1942.

10. Christie, A., and Peterson, J. C.: Pulmonary Calcification in Negative Reactors to Tuberculin, Am. J. Pub. Health **35**:1131-1147, 1945. Palmer, C. E.: Non-Tuberculous Pulmonary Calcification and Sensitivity to Histoplasmin, Pub. Health Rep. **60**:513-520, 1945.

11. Goddard, J. C.; Edwards, L. B., and Palmer, C. E.: Relationship of Pulmonary Calcification with Sensitivity to Tuberculin and to Histoplasmin, Pub. Health Rep. **64**:820-844, 1949.

12. Goddard.[11] Sontag, L. W., and Allen, J. E.: Lung Calcifications and Histoplasmin-Tuberculin Skin Sensitivity, J. Pediat. **30**:657-667, 1947.

REPORT OF CASES

Two cases of miliary nodules in patients with chronic mitral stenosis are reported:

CASE 1.—R. P., a 29 year old white unmarried woman, was admitted to Beth-El Hospital May 16, 1949, with complaints of dyspnea, pain in the left side of the chest and a cough productive of brownish sputum for the past month. She was indefinite about two attacks of rheumatic fever at the ages of 9 and 12 years but said that a definite diagnosis of rheumatic heart disease had been made at the age of 16, when she applied for a job. She remained asymptomatic until the age of 25. For the past four years she had had recurrent attacks of "colds," dyspnea,

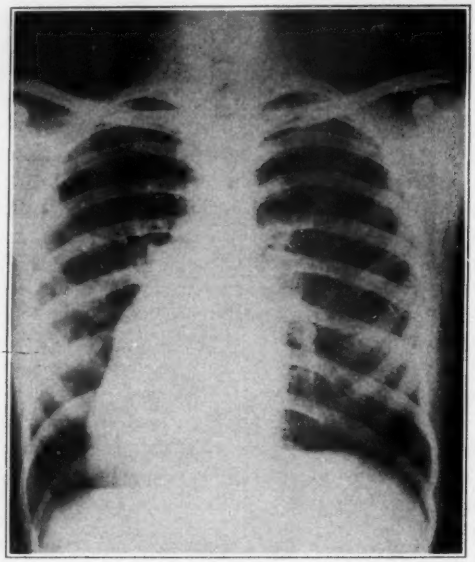

Fig. 1 (case 1).—"Soft" miliary nodules in the lung parenchyma in R. P.

pain in the joints and fever. No hemoptysis had occurred. The patient had been digitalized for short periods during this interval. On admission, she presented a presystolic and systolic murmur at the apex, fine bilateral basal rales, a blood pressure of 80 systolic and 50 diastolic, a liver palpable 8 cm. below the costal margin and no peripheral edema. The electrocardiogram was consistent with a defect of the mitral valve. Roentgenograms of the chest were taken on May 17, May 27, June 7 and June 21. They all presented a cardiac silhouette consistent with a double defect of the mitral valve (stenosis predominating), hilar congestion and irregular soft stippling of the lung parenchyma, particularly in the middle fields of the lungs (figs. 1 and 2). The patient's complaints disappeared on rest and administration of mercurial diuretics and digitalis, and she was discharged as improved on June 24.

Case 2.—H. C., a 45 year old white man, was admitted to the Beth-El Hospital on March 6, 1949, with hacking cough, dyspnea and hemoptysis. He had had an attack of rheumatic fever at the age of 5 years, and a diagnosis of rheumatic

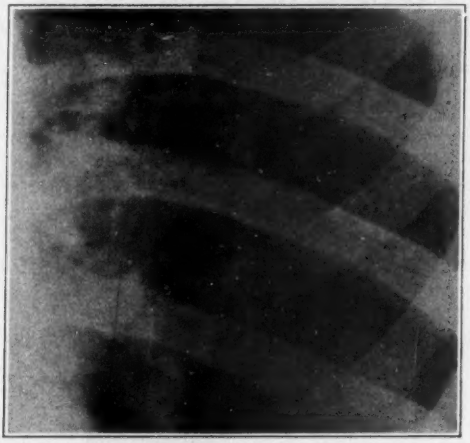

Fig. 2 (case 1).—Enlargement of the middle region of the right lung in R. P., demonstrating the "soft" nodules.

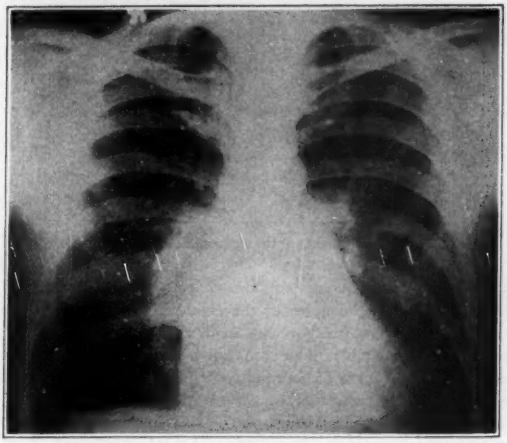

Fig. 3 (case 2).—"Calcific" nodules in the lung parenchyma in H. C.

heart disease had been made at the age of 16. He had worked hard as a glazier and had been relatively asymptomatic except for a mild chronic cough until the age of 35, when he required digitalization for a short time. He was again well

until the age of 41, when he noted progressive dyspnea, edema of the ankles and attacks of hemoptysis. These forced him to retire from work, and he had been unemployed for the four years previous to this report. On admission he showed fibrillation (the apical rate was 140 and the pulse rate 100) and a loud systolic murmur could be heard at the apex, at the left axilla and in the left interscapular region. There were scattered transient rales at the bases of both lungs. The liver was palpable 10 cm. below the costal margin; there was no edema of the ankles. The venous pressure was found to be 16 cm.; this rose to 22 cm. after pressure on the liver. The circulation time was 22 seconds arm to lung and 48 seconds arm to tongue. The electrocardiogram revealed signs suggestive of auricular

Fig. 4 (case 2).—Enlargement of the lower field of the left lung in H. C.

fibrillation and other changes consistent with chronic defect of the mitral valve and digitalis effect. The roentgenogram of the chest taken on his third hospital day revealed an enlarged cardiac shadow consistent with a double lesion of the mitral valve (stenosis predominating), hilar congestion and numerous calcific areas of density in the lower two thirds of both pulmonic fields (fig. 3 and 4). The original interpretation of the film was that of chronic productive tuberculosis associated with mitral disease and cardiac congestion. This impression was changed after the skin tests were completed. The patient showed a negative reaction to the tests with old tuberculin, histoplasmin and coccidioidin in dilutions of 1:100. He was discharged as improved on his eleventh hospital day, having been given routine care.

COMMENT

Two cases of pulmonary nodules associated with mitral stenosis are presented. We are of the opinion that the infrequency of this association is more apparent than real. Although the first patient exhibited the "soft" areas of infiltration and the second the "calcific" areas of density, according to the distinction maintained in the literature, we suggest that the conditions be interpreted as due to the same basic changes. These consist of a combination of hemosiderosis, fibrosis, chronic congestive changes and engorged vessels, with the calcification and ossification representing a more extreme reaction to the degenerative changes. The distinctions based on the varying radiopacity of the nodules are unnecessary, from the physiopathologic point of view.

The second case also serves to emphasize the point that not every case of pulmonary calcification is due either to tuberculosis or to histoplasmosis. Even though the majority are due to these two infections, skin testing can not be omitted if one wishes to achieve an accurate diagnosis.

CONCLUSIONS

1. Pulmonary nodules of varying degrees of density may be seen in roentgenograms of the chest of patients with long-standing mitral stenosis.

2. The diagnosis is usually made during the asymptomatic period or when the patient is in mild failure.

3. The use of routine roentgenograms of the chest is recommended to determine the exact frequency of this complication.

4. Patients with pulmonary areas of calcification should be given skin tests with histoplasmin and coccidioidin as well as with old tuberculin before a final diagnosis is made.

LUTEMBACHER'S SYNDROME ASSOCIATED WITH DEXTROCARDIA

IRVING INNERFIELD, M.D.
NYACK, N. Y.

AS SEPARATE and distinct conditions, dextrocardia and Lutembacher's syndrome can be considered unusual clinical entities. Certainly the coexistence of interauricular septal defect, mitral stenosis (Lutembacher's syndrome) and dextrocardia is sufficiently infrequent to warrant detailed analysis. A review of the medical literature for the past twenty-five years does not disclose any mention of this particular association of congenital cardiac anomalies. It therefore appears that this combination of dextrocardia and Lutembacher's syndrome is a unique one and warrants comment.

Observations on Cardiac Catheterization

	Oxygen Content, Volumes per Cent	Oxygen Saturation, per Cent
Superior vena cava	12.6	58
Inferior vena cava	15.8	73
Right auricle	14.2	66
Left auricle	19.6	91
Pulmonary vein	21.3	97
Femoral artery	18.8	89

REPORT OF A CASE

H. V., a 20 year old youth, presented himself for examination on July 14, 1949. The past history was entirely irrelevant except for an apparent predisposition to infections of the upper respiratory tract. The patient stated that he tired easily and was moderately dyspneic on exertion. He further stated that for many years he was aware of cardiac pulsations in the region of his right nipple.

The significant cardiac findings included a rough, rumbling diastolic murmur in the mitral area and a soft blowing systolic murmur in the first to third left interspaces at the left sternal border. The P wave in lead II was accentuated and split. The apex was palpated in the sixth intercostal space at the midclavicular line. No thrills were present at either base or apical areas. A roentgenogram (fig. 1)

From the Department of Medicine, New York Medical College, Flower and Fifth Avenue Hospitals.

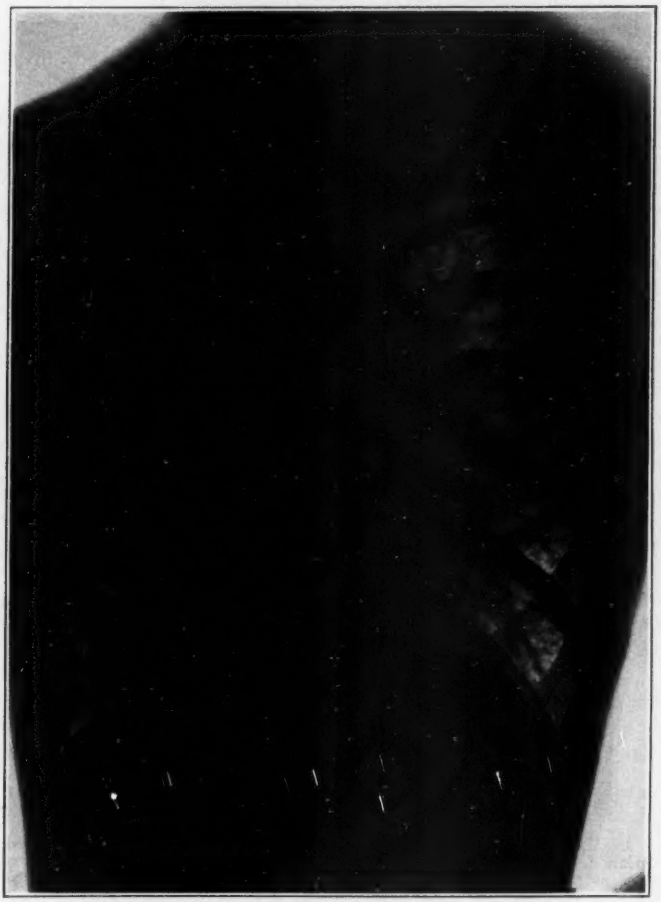

Fig. 1.—Roentgenogram of the chest showing dextrocardia, globular heart shadow, prominent pulmonary artery, thickened hazy pulmonary shadows and prominent hilar vessels. The left diaphragmatic leaflet is distinctly elevated. The stomach (identified by the gas bubble and fluid level) is in normal position, thus ruling out situs inversus.

revealed dextrocardia, a greatly enlarged right ventricle, a small aorta, a markedly prominent pulmonary artery and engorged hilar vessels. Fluoroscopic examination showed definite hilar dance. The observations on venous catheterization (table) were considered compatible with a diagnosis of interauricular septal defect. The blood pressure was 110 systolic and 90 diastolic; the erythrocyte count,

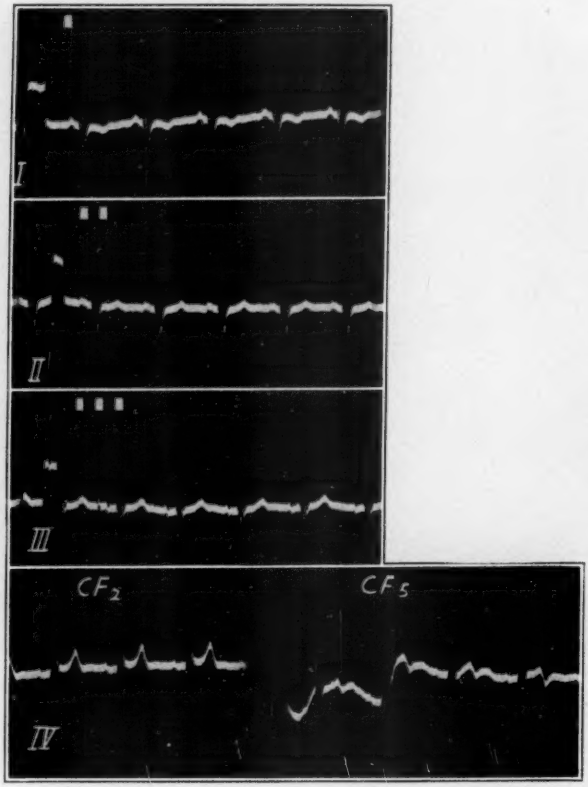

Fig. 2.—Electrocardiogram showing regular sinus rhythm, pronounced right axis deviation, slurred QRS complexes and an intraventricular conduction defect.

4,600,000, and the hemoglobin concentration, 79 per cent. Urinalysis revealed nothing of significance, and serologic tests elicited negative reactions. The nail beds appeared cyanotic, and questionable clubbing of the fingers was observed. The blood was sterile on culture.

The chief electrocardiographic findings were pronounced right axis deviation and an interventricular conduction defect (fig. 2).

COMMENT

The first case of interauricular septal defect and mitral stenosis was reported by Martineau [1] in 1865. The subsequent paucity of case reports in the earlier medical literature can be appreciated from the fact that when McGinn and White [2] reviewed the subject in 1933, adding a case of their own, the total number of cases was 24. Since then, isolated cases have been reported.

This syndrome is not incompatible with longevity. Firket [3] in 1880 described the case of a 74 year old woman who had survived eleven pregnancies. Lutembacher reported another case, that of a woman aged 61, who had uneventfully gone through seven pregnancies. On the other hand, 11 of the 24 patients in McGinn and White's series died at or before the age of 30; the average age at death was 35.

In cases of interauricular septal defect mitral stenosis is usually acquired early. Lutembacher, postulating a congenitally stenosed valve, stated the belief that the elevation of pressure in the left auricle prevented proper closure of the foramen ovale and hence produced a reversal of the usual flow through the fetal heart.[4] Firket expressed the opinion that the combination of congenital deformity of the mitral valve and abnormality of the interauricular septum was a fortuitous occurrence which served to safeguard against the pulmonary congestion that would result from the mitral lesion alone.[3]

Dressler and Roesler are proponents of the theory that an increase in pressure in the left auricle, such as undoubtedly occurs after birth, would favor closure of the foramen ovale because of the obliquity of the canal.[5] Furthermore, they expressed the belief that a small congenital interauricular septal defect complicated by an acquired mitral stenosis would in time become greatly enlarged because of dilatation resulting from the increase in pressure within the left auricle. McGinn and White expressed agreement with these authors.[2]

Maude Abbott made the interesting observation that "atrial septal defects are frequently associated with abnormalities in the structure of the mitral valve leaflets." [6] This would suggest the possibility that dis-

1. Martineau: Sur un cas de rétrécissement mitral avec persistance du trou de Botal, Bull. Soc. d. sc. med. **12**:202, 1865.

2. McGinn, S., and White, P. D.: Interauricular Septal Defect with Mitral Stenosis, Am. Heart J. **9**:1, 1933.

3. Firket, C.: Examen anatomique d'un cas de persistance du trou ovale de Botal, Ann. Soc. méd.-chir. de Liége **19**:188, 1880.

4. Lutembacher, R.: De la sténose mitrale avec communication interauriculaire, Arch. d. mal. du cœur. **9**:237, 1916.

5. Dressler, W., and Roesler, H.: Vorhofseptumdefekt kombiniert mit Mitralstenose und aurikulären Leberpuls, Ztschr. f. klin. Med. **112**:412, 1930.

6. Abbott, M. E.: Atlas of Congenital Cardiac Disease, New York, American Heart Association, Inc., 1936, p. 58.

turbed stress-strain phenomena may more readily predispose to rheumatic endocarditic changes. In 1936 Abbott compiled 1,000 cases of congenital heart disease proved at autopsy and reported 29 cases of "isolated" dextrocardia. Eleven of these were cases of true dextrocardia with situs inversus; 10 were instances of dextrocardia without situs inversus but with inversion of the cardiac chambers; 8 were cases of dextrocardia with neither situs inversus nor inversion of the cardiac chambers. In no instance was the association of dextrocardia with the Lutembacher syndrome recorded.

In the fetal circulation a large proportion of the blood flows from the right auricle via the normal opening into the left auricle and thus to the left ventricle and out into the peripheral circulation. After birth, with the expansion of the lungs, the adult type of circulation is set in progress and, the auricular pressures being about equal, normal blood flow is maintained even though there may be a partial defect in the septum.

If a change such as mitral stenosis ensues, the left auricular pressure rises and blood is forced from the left to the right auricle, with the result that the blood is sent through the pulmonary circuit a second time. Consequently, the right side of the heart does more work than the left, and dilatation and hypertrophy of the right chambers take place, along with enlargement of the pulmonary artery and its branches. The left ventricle and aorta remain small. In failure of the right ventricle, there is further rise in right auricular pressure, thereby leading to a reversal of flow from right to left. The latter sequence of events explains the occurrence of tardive cyanosis (*cyanose tardive*) found so often in patients with a deficiency of the auricular septum.

Clubbing is rarely encountered in persons with uncomplicated interauricular septal defects. Taussig, Harvey and Follis mentioned the characteristic appearance of these patients, who have delicate, semitranslucent skin and are of slender build, with light bony structure.[7]

Thrills may or may not be observed. When present, they may be systolic or diastolic and usually are felt in the pulmonic region. Murmurs are inconstant. The most frequent finding is a systolic murmur, best heard at the third left interspace. This systolic murmur may closely simulate that of interventricular septal defect, but it is not so constant, is usually higher and is not so intense.

Because of the hypertrophy and dilatation of the right auricle and ventricle, which causes a counterclockwise rotation of the organ, the heart is enlarged both to the right and to the left of the sternum. Pulsation of the liver and of the cervical veins is observed when a relative tricuspid insufficiency is present.

7. Taussig, H. B.; Harvey, A. M., and Follis, R. H., Jr.: The Clinical and Pathological Findings in Interauricular Septal Defects: A Report of Four Cases, Bull. Johns Hopkins Hosp. **63**:61, 1938.

The electrocardiogram usually shows a right ventricular preponderance and high P waves. Graybiel and White found the most pronounced right ventricular preponderance in three conditions: dextrocardia, auricular septal defect and the tetralogy of Fallot.[8]

The most reliable antemortem findings are those elicited by roentgenographic and roentgenoscopic examinations. These findings include an enlarged heart (mostly confined to the right side), a very small aortic knob, greatly enlarged pulmonary artery and wide hilar shadows which frequently pulsate (hilar dance).

In 1941 Bedford, Papp and Parkinson[9] studied a group of patients with Lutembacher syndrome from the standpoint of compensatory hemodynamic alterations. They observed that the existence of auricular septal defect provided a shunt for the excess blood in the left auricle, thereby significantly lessening the left intra-auricular pressure. This phenomenon adequately explains the well established clinical observation that patients with Lutembacher syndrome are not subject to episodes of acute pulmonary edema or hemoptysis. The escape of blood backward through the atrial opening undoubtedly exerts an equilibrative mechanism against the eventual development of pulmonary hypertension. This sequence of events, however, places an extra burden on the right chamber of the heart.

Auricular fibrillation also has been noted to develop at a later age in persons with the Lutembacher syndrome than in persons with uncomplicated mitral stenosis. This fact further suggests an element of protection for the left auricle.

It is interesting to note that Bland and Sweet[10] have recently devised an operation for the creation of a venous shunt in the surgical treatment of advanced mitral stenosis. In this particular operation an extracardiac shunt is created, anastomosing the azygos vein to the dorsal segment of the right inferior pulmonary vein. In other words, this type of operation represents a surgical attempt to duplicate the salutary circulatory adjustments provided for by nature in cases of interauricular septal defect.

SUMMARY

A case of interauricular septal defect combined with mitral stenosis (Lutembacher's syndrome) associated with dextrocardia is reported. It is apparently the first case of this kind to be put on record. Pathogenesis, clinical features and diagnostic considerations are discussed.

58 North Broadway, Nyack, N. Y.

8. Graybiel, A., and White, P. D.: Electrocardiography in Practice, Philadelphia, W. B. Saunders Company, 1941, p. 78.

9. Bedford, D. E.; Papp, C., and Parkinson, J.: Atrial Septal Defect, Brit. Heart J. **3**:37, 1941.

10. Bland, E. F., and Sweet, R. H.: A Venous Shunt for Advanced Mitral Stenosis, J. A. M. A. **140**:1259 (Aug. 20) 1949.

Progress in Internal Medicine

SYPHILIS

A Review of the Recent Literature

HERMAN BEERMAN, M.D.
LESLIE NICHOLAS, M.D.
MINERVA S. BUERK, M.D.
AND
WILLIAM T. FORD
PHILADELPHIA

(Continued from Page 358)

CEREBROSPINAL FLUID

The cerebrospinal fluid examination has assumed added importance with the advent of penicillin therapy. Whether one should rely on changes in the spinal fluid alone or on a combination of the fluid and clinical changes has not been settled, and there are syphilologists and neurologists who favor both sides. Dattner,[98] of Bellevue Hospital, New York, is one who relies largely on the changes in the cerebrospinal fluid. He believes that in neurosyphilis evaluation the results of examination of cerebrospinal fluid offers additional information as to the character of the underlying processes. Of especial value are the cell count, determination of total proteins, and colloidal mastic test.

Pleocytosis is indicative of activity of the pathologic processes in the nervous system. Arrest of the syphilitic process is quickly followed by a return of the cell count to normal and occurs in all successfully treated patients. If the syphilitic process is definitely arrested, there is no recurrence of the pleocytosis. Pleocytosis is the best criterion of the activity of syphilis of the central nervous system. The next best guide for determining the syphilitic process is the estimation of total protein values. These values follow the intensity of the inflammatory-degenerative process. Effective treatment manifests itself by a gradual decrease to normal, whereas relapse is marked by increasing amounts of total protein on repeated tests. Additional support in estimating the efficacy of treatment is given by the colloidal gold test. Though originally designed to differentiate between the various globulins and albumins constituting the total proteins, the constant color changes of the gold sol, which are expressed in numerical values, can be totaled and furnish a quantitative standard. After successful treatment there is

98. Dattner, B.: Significance of Spinal Fluid Findings in Neurosyphilis, Am. J. Med. **5**:709-711 (Nov.) 1948.

change not only in the character of the curve but also in the sum total of the color figures. A positive Wassermann reaction of the spinal fluid does not prove activity of the syphilitic process, but, with an associated pleocytosis and increased protein, activity must be assumed. Activity must not be assumed on a positive complement fixation alone. Repeated examinations of the spinal fluid, including estimation of cell count, proteins, Wassermann test and the new Lange colloidal gold test should be made to evaluate progress of neurosyphilis.

Cerebrospinal Fluid in Multiple Sclerosis.—Frequently the clinical findings in multiple sclerosis mimic those of neurosyphilis, and when the results of the cerebrospinal fluid study are also equivocal much diagnostic confusion results.

The syndrome of multiple sclerosis is diagnosed on the basis of the findings in five laboratory examinations of cerebrospinal fluid correlated with the clinical data: 1. The cerebrospinal fluid must be clear and colorless. 2. There must be no reaction in the complement fixation test for syphilis with both spinal fluid and blood. 3. The cell count and cell types may be normal (less than 2 mononuclears per cubic millimeter) or slightly increased (5 to 10 mononuclears per cubic millimeter). Polymorphonuclear leukocytes are present very rarely in an acute exacerbation. 4. The concentration of total protein is, on the average, slightly increased (40 to 50 mg. per hundred cubic centimeters) but frequently lies within normal limits (15 to 30 mg. per hundred cubic centimeters). 5. The colloidal gold test characteristically reveals a type D curve (paretic or parenchymatous) strong to minimal. Other types of curve may be encountered. The clinical data comprise signs, symptoms and course indicative of multiple sclerosis. In the opinion of Lange and Harris,[99] the syndrome of multiple sclerosis cannot be established conclusively unless neurosyphilis has been excluded by the absence of a reaction in the quantitative complement fixation test of Wadsworth with use of cardiolipin antigen, which is superior in sensitivity and specificity, coupled with a knowledge of the clinical facts of the case. The quantitative colloidal gold reaction provides the only relevant positive laboratory finding. Comparisons of colloidal gold reactions in neurosyphilis and multiple sclerosis and of findings in acute exacerbation of multiple sclerosis and in neurosyphilis are presented in detail.

Mailed Spinal Fluid Specimens.—In certain communities it is necessary to send samples of cerebrospinal fluid some distance away for examination. This engenders definite limitations in the results of the examination of such fluids.

99. Lange, C., and Harris, A. H.: Interpretation of Findings in Cerebrospinal Fluid: III. Syndrome of Multiple Sclerosis, Am. J. Clin. Path. **19**:16-24 (Jan.) 1949.

Cannefax and his group,[100] medical officers of the Hot Springs Medical Center, Hot Springs, Ark., had observed over a period of years that follow-up spinal fluid specimens received by mail frequently showed results of the total protein and Kolmer test to be higher than the results obtained on the same patient while under treatment at the Medical Center. Subsequent rechecks at the Medical Center prior to retreatment showed values comparable to the original findings. These considerations served as a stimulus for conducting this study. Specimens of spinal fluid submitted for study were divided into three parts. The first portion of spinal fluid, the control, was placed in a sterilized tube and examined within two hours after puncture. The second portion was placed in a sterile rubber-stoppered vacuum-sealed tube. The third specimen was placed in a sterile tube and stoppered with a nonsterile cork stopper. The second and third specimens were mailed into the center at varying intervals, ranging from two to nine days. The study was comprised of one hundred and six spinal fluid specimens. It demonstrated that the total protein values in spinal fluids are generally higher in mailed specimens than in identical specimens tested immediately. The total protein values show a greater elevation in spinal fluids mailed in nonsterile cork-stoppered tubes than in specimens mailed in sterile vacuum type tubes. The study also showed that both a short time factor and the use of sterile containers are necessary in order to insure reliable results in Kolmer tests on mailed spinal fluid specimens. The control portions of the specimens were 88.7 per cent negative; the portions mailed in the vacuum-sealed containers were 87.7 per cent negative; the portions mailed in nonsterile cork-stoppered containers were only 45.3 per cent negative.

Bossak and his colleagues[101] describe a new test procedure employing 10 per cent trichloroacetic acid as a protein precipitant and they present comparative findings obtained with this and the Denis-Ayer sulfosalicylic acid method on prepared mixtures of albumin and globulin and also a spinal fluid of selected donors. The precipitation test employing trichloroacetic acid is extremely simple. The 10 per cent trichloroacetic acid is merely added to the specified amount of spinal fluid and the contents mixed. The fluid is then placed in the cuvette of a photoelectric colorimeter and the percentage of transmission at a wavelength of approximately 420 microns determined. This percentage is then converted to milligrams of protein by reference to a calibration chart.

100. Cannefax, G. R.; Parkhurst, G. E., and Bowman, R. W.: Comparative Studies on Mailed Spinal Fluid Specimens, J. Ven. Dis. Inform. **30**:11-14 (Jan.) 1949.

101. Bossak, H. N.; Rosenberg, A. A., and Harris, A.: A Quantitative Turbidimetric Method for the Determination of Spinal Fluid Protein, J. Ven. Dis. Inform. **30**:100-103 (April) 1949.

The sulfosalicylic acid procedure gives good results when the albumin-globulin ratios are normal. Changes in the ratio alter total protein values by this method. The trichloroacetic acid method gives results that reflect true protein concentrations regardless of the albumin-globulin ratios.

Flodén [102] stresses the importance of an accurate estimation of cerebrospinal fluid protein fractions for the proper diagnosis of organic lesions of the central nervous system and meninges. Using the method described by Izikowitz, Flodén found abnormalities in cerebrospinal fluids which appeared normal on examination with older methods (Pandy and Nonne-Apelt tests).

Cardiolipin-Lecithin Antigen.—The Venereal Disease Research Laboratory [103] staff has devised a rapid slide and tube flocculation test using a cardiolipin-lecithin antigen. The antigen is rapidly prepared and stable, but the tests were not especially adapted to testing of spinal fluid. The purpose of this paper was to describe a companion procedure which is called the Venereal Disease Research Laboratory spinal fluid test. The methods for testing serum do not lend themselves to testing spinal fluid because of the quantitative and qualitative differences of the two substances; e. g., the protein components and amount of reacting components differ. In designing this new technic several factors could influence the test reactivity: (1) the ratio of spinal fluid to antigen emulsion, (2) the concentration of sodium chloride and (3) the period of mechanical shaking prior to centrifugation. The antigen employed is the cardiolipin-lecithin antigen prepared as previously described. A comparative study on 633 spinal fluids employing the Kolmer, Kahn, Eagle and Kline cardiolipin antigens, as well as the new technic employing the cardiolipin-lecithin antigen, shows that the results obtained with the latter antigen are comparable to those obtained with other antigens.

Kline and Suessenguth [104] also describe the detailed technic of the standard Kline test on cerebrospinal fluid employing the cardiolipin-lecithin antigen. Antigen mixtures of different lots of standard cardiolipin and of one lot of standard lecithin gave similar results on slide tests for syphilis. Antigen mixtures of different lots of standard lecithin and of one lot of standard cardiolipin gave results of variable sensitivity. Different lots have variable behaviors. Therefore it is necessary to

102. Flodén, C. H.: Fractional Protein Determination in Spinal Fluid in Various Stages of Syphilis, Acta dermat.-venereol. **28**:403-411, 1948.

103. Rosenberg, A. A.; Harris, A., and Harding, V. L.: A Macroflocculation Spinal Fluid Test Employing Cardiolipin-Lecithin Antigen, J. Ven. Dis. Inform. **29**:359-361 (Dec.). 1948.

104. Kline, B. S., and Suessenguth, H.: Standard Kline Test of Cerebrospinal Fluid for Syphilis, Employing Cardiolipin-Lechithin Antigen, Am. J. Clin. Path. **19**:274-277 (March) 1949.

titrate each lot of lecithin with standard cardiolipin for the determination of the optimum ratio for use in the preparation of the slide test emulsions. Further, a more satisfactory formula for the preparation of antigen emulsion for the spinal fluid slide test is necessary. Twelve new formulas with specified amounts of antigen mixture of four lots of cardiolipin, five lots of lecithin and different quantities of cholesterol, water and salt solution were tested. The formula giving best results on eight hundred and fifty spinal fluids is described.

Colloidal Gold.—The gold sol previously employed in the colloidal gold reaction has been relatively unstable. Lange and Harris [105] describe methods used in preparing stable sols and the technics that have been developed for selecting sols of optimum sensitivity. With the method decribed in detail in this paper, one can prepare a stabilized colloidal gold sol that is superior to any colloidal gold preparation or colloidal substitute thus far described in regard to simplicity of preparation, sensitivity, stability and reproducibility.

Lumbar Puncture Headache.—Pickering [106] says that it is not uncommon for a headache to develop after puncture of the spinal theca. Pain may be more or less generalized over the calvarium but is often especially severe at the back of the head and may spread into the neck, shoulders or back. The neck may feel stiff. The feature which distinguishes this headache from all others is its exacerbation when the patient sits up and its relief when he lies down. The headache may begin a few hours to a few days after the puncture, and it usually lasts twenty-four hours or more. The author reviews observations on 11 patients with lumbar puncture headache, in 7 of whom spinal pressure was measured. Cerebrospinal fluid pressure in the horizontal posture was observed to be about atmospheric in 6 cases and within the lower limit of normal in 1. In all these 7 cases injection of 30 to 50 cc. of isotonic sodium chloride solution, sufficient to restore the pressure to the normal or upper normal range, abolished the headache. Headache was invariably increased by sitting up and relieved by lying down. It was usually increased by compressing the jugular veins in the neck and by shaking the head. Not infrequently the headache throbbed with the pulse and in about half the cases was relieved by compression of the carotid artery in the neck. Lumbar puncture headache is ascribed to caudad displacement of the base and posterior parts of the brain with tension on the neighboring structures, particularly the tissues around the large arteries at the base.

105. Lange, C., and Harris, A. H.: Stabilized Citrate Gold for Use in the Colloidal Gold Reaction, J. Ven. Dis. Inform. **29**:265-269 (Sept.) 1948.

106. Pickering, G. W.: Lumbar Puncture Headache, Brain **71**:274-280 (Sept.) 1948.

Iron in Cerebrospinal Fluid.—Greif [107] studied the plasma iron tolerance curves of patients with early and with late syphilis and compared these curves with those obtained on patients with other infections and anemias. Observations were also made on the iron concentration in human cerebrospinal fluid and in plasma of syphilitic and nonsyphilitic rabbits. Most patients with syphilis, both early and late, showed a significant rise in plasma iron concentration following oral administration of ferrous sulfate. Patients with other infections or with anemia also showed a significant rise in the plasma iron concentration. Therefore, no diagnostic value could be attached to the tolerance curves in syphilitic persons. Determinations of iron in the spinal fluids of 18 patients with syphilis showed no correlation between concentration of iron in the cerebrospinal fluid and other pathologic changes in the fluids. Concentrations of iron in the serums of 4 syphilitic rabbits were slightly lower than those of the serums of 4 normal rabbits.

CLINICAL MANIFESTATIONS

Race.—The effect of race on the course and manifestations of syphilis is an important consideration in clinical syphilology and one worthy of further controlled experimental study. Frazier and Li's [4] monograph on "Racial Variations in Immunity for Syphilis" has already been mentioned. All syphilologists well versed in the literature will recall in this connection the early paper by Fox [108] and Hazen's [109] contributions to this subject. The following papers throw interesting sidelights on this problem.

In an address to the Postgraduate Assembly of Negro Physicians at Prairie View, Texas, Frazier [110] presented an interesting, though general, paper on the problem of syphilis in the Negro. He discussed the earlier age of infection and the promiscuity of the Negro and the racial localization of cardiovascular and nervous system syphilis.

In an evaluation of race and disease Lewis [111] discusses several diseases among Negroes to illustrate the fact that race alters the clinical picture. These diseases include tuberculosis, syphilis cancer, sickle cell anemia and fibrosis diathesis (keloid and fibromyoma of the uterus).

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107. Greif, R. L.: Plasma and Cerebrospinal Fluid Iron Concentration Studies in Syphilitic and Nonsyphilitic Patients, Am. J. Syph., Gonor. & Ven. Dis. **32**:337-344 (July) 1948.

108. Fox, H.: Observations on Skin Diseases in the Negro, J. Cutan. Dis. **26**:67-79 (Feb.); 109-121 (March) 1908.

109. Hazen, H. H.: Syphilis in the Negro: Handbook for the General Practitioner, Ven. Dis. Inform., 1942, supp. 15, pp. 1-96.

110. Frazier, C. N.: The Problem of Syphilis in the Negro Race, Texas Rep. Biol. & Med. **6**:192-199, 1948.

111. Lewis, J. H.: Race and Disease, Proc. Inst. Med., Chicago **17**:112-118 (May 15) 1948.

Lewis states that both tuberculosis and syphilis have a typical reaction in virgin soil; both are modified in the course of time by development of community resistance, and both are intimately related to environmental conditions. Syphilis was not introduced to all races simultaneously. It appears that the disease started in Africa three to four hundred years after its known appearance in Europe. Like the picture of tuberculosis in Negroes, the picture of syphilis is also changing in this race. Neurosyphilis is apparently increasing; bone and visceral syphilis seem to be decreasing; syphilis of the cardiovascular system will probably diminish, and a general resistance to invasion by spirochetes should develop, resulting in a lowered prevalence of the disease. As the disease grows older in all races, there may be a tendency toward the establishment of a universal uniformity in type.

According to De Mello,[112] in 1940 it was observed that the rate of infection with syphilis was increasing among local Africans in Kenya. Whether among the civilized peoples of the world or among the primitive population of Africa, venereal diseases will perhaps remain a difficult problem. The clinical manifestations of yaws and syphilis are closely allied to each other and often cause great difficulty in the diagnosis. The rash is sometimes not so evident in the dark skin, and in every case the African comes for treatment when the disease is well over the secondary stage and, consequently, the reaction of the blood is strongly positive. The commonest manifestations are mucous patches affecting the tongue, tonsils, palate, gums, vulva, groin and the region below the fold of the breasts. The majority of patients treated are women who discontinue treatment in the middle of the course and return again after two months with recurrence of the mucous patches. It is believed that African children with congenital syphilis do not live long. They are usually born marasmic, with a huge spleen and liver and often with inflamed joints. They do not respond to any treatment and usually die within three months. Treatment of the African is difficult because it is hard to make him realize that he must avoid exposing himself to the dangers of venereal disease while under treatment. Intolerance to the drugs is another problem. The liver is readily susceptible to the toxicity of arsenic and bismuth.

Willcox [113] compares the incidence of venereal diseases in 53 West Africans and an equal number of Europeans in a venereal disease clinic in London. Sixty and four-tenths per cent of the West Africans, as compared with 30.2 per cent of the Europeans, had syphilis or gonorrhea or both in a communicable form on the occasion of their first visit to the

112. De Mello, J.: Syphilis in Africans, East African M. J. **25**:14-17 (Jan.) 1948.

113. Willcox, R. R.: Venereal Disease and the West African in London, J. Roy. Army M. Corps **92**:168-172 (April) 1949.

clinic. The West Africans admitted 43 previous venereal infections, which was nearly double the 23 infections previously contracted by the Europeans.

In a report on the results of the Wassermann test on 1,000 blood specimens taken from Bantu men, O'Malley and Wilson [114] found that the widely held opinion as to a high syphilis rate in this group is a mistaken one. The number of positive blood specimens found was 74, giving a percentage of 7.4. The tests were carried out over a period of sixteen months. The subjects were all members of the Bantu race, which inhabits the southern portion of Africa. These people are pastoral in habit and live under tribal conditions. The findings are classified according to marital state, age, tribe and previous residence in an urban area. It appears that the age group most affected was that including persons under 20 years of age. There was no significant statistical difference between the married and the unmarried groups. Results do not support any definite conclusion on previous contact with urban social conditions. On the other hand, several random studies of syphilis in the native population of South Africa reviewed by Kark [115] revealed an incidence of 23.6 per cent in urban groups and 23.28 per cent in rural groups. In the towns the number of unattached men is four times as great as that of attached men. Over and above this, a large number of these unattached men are not permanent residents in the town. When there is such a high proportion of virile men as compared with women, the results are likely to be undesirable. The men will seek their social and sexual life in brothels. These unattached men make up the largest social group in urban areas because of the development of the gold and diamond mines. Transient laborers are imported from rural areas. The author concludes that from the stabilization of urban areas will emerge a set of mores which, among other benefits, will gradually control the spread of syphilis.

Cook [116] presents evidence contradicting the general belief that neurosyphilis is rare in the Negro and less severe in tropical climates. On the basis of an unselected group of patients obtained largely through a program of mass blood testing on the cosmopolitan population (chiefly Negro) in Trinidad, British West Indies, as well as the study of some East Indian, white and Chinese persons he concludes that neurosyphilis is not rare in the tropics; the rate for neurosyphilis was found to be 20 per cent among unselected syphilitic patients. It may be that sympto-

114. O'Malley, C. K., and Wilson, A. J.: Results of the Wassermann Test in an Unselected Bantu Group, South African M. J. **23**:73-75 (Jan. 29) 1949.

115. Kark, S. L.: The Social Pathology of Syphilis in Africans, South African M. J. **23**:77-84 (Jan. 29) 1949.

116. Cook, M. J.: Neurosyphilis in the Tropics, J. Ven. Dis. Inform. **29**:204-207 (July) 1948.

matic neurosyphilis is less severe in natives of the tropics than in North Americans and Europeans. The severity of neurosyphilis may be somewhat tempered by the presence of endemic malaria, since malarial rates of 20 to 80 per cent existed in some areas from which the patients were drawn. Severe neurosyphilis is frequent enough to warrant early attention in all cases.

Unsuspected Syphilis in Older Persons.—According to Thewlis and Gale,[117] unsuspected, unadmitted syphilis is rather common in old age. Syphilis should always be supected in an old person with obscure illness. Tertiary syphilis may show up in persons infected thirty or forty years before. The first signs of hereditary syphilis may not appear until after the age of 50. The serologic and spinal fluid examinations may not yield any clue. Syphilis may cause symptoms suggesting almost any known disease. It may produce a background against which hereditary epilepsy shows up, causing cardiovascular symptoms. Multiple tests for syphilis are essential in the diagnosis of chronic illnesses. Many conditions may be caused by unsuspected syphilis. Among these are gallstones, peptic ulcer, appendicitis, bronchiectasis, epileptiform seizures, asthenia, hypertension, atrophic or hypertrophic arthritis, carcinoma, disease of the central nervous system, long continuous fever, endarteritis, diabetes and other diseases. Ulcers of the leg are commonly found. Serologic tests may be baffling. The Wassermann reaction of the spinal fluid may be positive while the colloidal gold and other tests give negative results. Older clinicians used potassium iodide internally and injections of red mercuric iodide. This treatment often proved satisfactory. Penicillin in large doses (5,000,000 to 8,000,000 units in divided doses) may be given to an ambulatory patient. One must always be prepared for a Herxheimer reaction in these cases. It is safer to begin treatment with iodides and then to give a bismuth compound, followed by penicillin. In treating syphilitic insufficiency of the coronary artery and syphilitic aortitis, iodides and bismuth compounds are employed. A febrile reaction within twenty-four hours after treatment may be disregarded. The patient must be kept under observation for the remainder of his life. Discovery of old syphilis and proper therapy may prolong life and save much suffering.

Paroxysmal Cold Hemoglobinuria.—Becker [118] presents a new case and a comprehensive review of the literature on the syphilitic type of paroxysmal cold hemoglobinuria, embracing 37 cases reported since 1930. Paroxysmal cold hemoglobinuria is a symptom complex having

117. Thewlis, M., and Gale, E. T.: Unsuspected Syphilis in Older Persons, Geriatrics **3**:335-343 (Nov.-Dec.) 1948.

118. Becker, R. M.: Paroxysmal Cold Hemoglobinurias, Arch. Int. Med. **81**: 630-648 (May) 1948.

two separate and distinct etiologic bases. Syphilitic paroxysmal cold hemoglobinuria is caused by a cold-warm hemolysis in a small percentage of patients with syphilis. A second, nonsyphilitic, type is cold hemagglutination paroxysmal hemoglobinuria observed in nonsyphilitic persons who have high titers of cold hemagglutinins. In the blood of patients with syphilitic paroxysmal cold hemoglobinuria is a circulating hemolysin which with complement is fixed to the red cells when there is exposure to cold. On subsequent warming of the patient, the hemolysin with the aid of complement hemolyzes red cells of the blood. If hemoglobinuria exceeds the renal threshold, the patient passes cherry red urine. Sweat, fever, abdominal cramps, nausea, weakness, headache, backache and vomiting may be accompanying signs. Occasional urticaria occurs. The paroxysms last one to two hours, though the red urine may persist for four to ten hours. A transient leukopenia is followed by leukocytosis. If attacks are frequent, the patient is weak and anemic. It has been proved by absorption tests that hemolysin is entirely distinct and separate from reagin. Cold urticaria observed in syphilitic cold hemoglobinuria is due to a substance called dermolysin which injures cells of the patients on exposure to cold followed by warming. Of the 38 patients whose cases are reported, 10 were children, all over 6 months of age. With the exception of 1, all had positive serologic reactions for syphilis. In all cases there was no evidence of active syphilitic infection clinically.

EARLY SYPHILIS

Blood Transfusion Syphilis.—According to Arzt,[119] the percentage of transmission of syphilis by blood transfusion is not known, but one infection in four thousand transfusions may be assumed to be approximately correct for certain countries in certain times. The process of infection with T. pallidum by transfusion differs from that by the cutaneous route in that there is no filtration through the lymph nodes and the infective material is much more massive, considering the transfusion of 300 to 500 cc. of blood. The most dangerous donors are persons in the first incubation period, in the absence of any clinical symptoms and serologic proof. The right selection of the donor is the essential point in the problem of prevention of syphilis by blood transfusion. Persons with serologically latent syphilis should be rejected. Professional blood donors should be preferred to occasional donors among relatives of the patient. Professional donors are examined first on registration and have to undergo regular control examinations by a venereologist. Immediately preceding the transfusion a renewed

119. Arzt, L.: Die Bluttransfusionssyphilis, Wien. klin. Wchnschr **61**:105-108 (Feb. 18) 1949.

clinical, and if possible serologic, examination, at least with a rapid reaction, should be made. Donors with serologically negative reactions who present symptoms from which syphilis may be expected and particularly donors with negative reactions with manifestations of any kind at the genitals should be rejected. The risk of transmission of syphilis may be reduced by the use of blood or serum treated with sodium citrate and preserved by refrigeration instead of fresh blood; the donor of the blood which is to be preserved should be subjected to a Wassermann test.

Infectivity of Blood and Spinal Fluid.—A study was made by Frazier and Pian [120] in the years 1933 to 1941 in Peiping, China, on the blood and spinal fluid of 46 Chinese patients (38 male and 8 female) to determine the frequency with which T. pallidum is present in the cerebrospinal fluid concurrently with its presence in the blood stream early in the disease. The blood and cerebrospinal fluid of the 46 patients, all of whom presented active signs of secondary syphilis, were inoculated into rabbits and tested for infectivity. The method of inoculation is described. It was found that 35 (76.1 per cent) of the blood inoculations produced infection in the rabbits. When the spinal fluids of the patients were transferred to the testes of rabbits 9 (19.6 per cent) positive inoculations resulted, all from male patients. It was concluded that infection of the blood in early syphilis does not indicate infection of spinal fluid. However, infection of the spinal fluid is accompanied with infection of the blood. There was no correlation between a particular clinical lesion and infectivity of the spinal fluid, although the values of positive inoculations from 40 per cent of patients with alopecia, as compared with 13.8 per cent from patients with no alopecia, approached statistical significance; the difference, however, is within the range of sampling error. In 14 patients who had infections of less than three months' duration organisms were not isolated from the spinal fluid, whereas 4 of 15 patients with infections of three to four months' duration had infectious fluids. In 2 patients with secondary manifestations of not more than two weeks' duration the spinal fluid was found to contain virulent organisms.

Asexual Syphilis in Children.—Eisenberg, Plotke and Baker [121] attempt to demonstrate that the incidence rate of asexually acquired syphilis in children is much higher than has previously been suspected. Smith reported an incidence of asexual syphilis in children as 1 per cent in his series of 125 cases collected over a period of seventeen years.

120. Frazier, C. N., and Pian, H. C.: Relative Infectivity of Blood and Cerebrospinal Fluid in Secondary Syphilis (China), Am. J. Med. **6**:443-448 (April) 1949.

121. Eisenberg, H.; Plotke, F., and Baker, A. H.: Asexual Syphilis in Children, J. Ven. Dis. Inform. **30**:7-11 (Jan.) 1949.

The cases considered in this study were observed during the year 1947 at the Chicago Intensive Treatment Center. There were 20 cases of secondary syphilis occurring in children under 10 years of age; it was determined that these patients were familial or asexual contacts. Of this group, 16 were girls and 4 boys. The average age was below 5 years. Four children were siblings from two different families. The incidence rate was 2.8 per cent of the total group of 721 patients with secondary syphilis. In all cases one member of the household or family in close relationship with the child had received a diagnosis of secondary syphilis. None of the children showed a primary lesion; 15 children had lesions positive for spirochetes on dark field examination, while all 20 had positive serologic reactions. Overcrowded home conditions and lack of education in hygienic matters appear to be conducive to development of asexual syphilis in children. This group of authors recommend that children in families in which a member has early infectious syphilis should be followed serologically for a period of three months, since several of their cases were found in this manner. The authors also stress the education of the patient to prevent this type of infection.

Primary Syphilis Without Clinical Symptoms.—During the German occupation of Brussels in 1940 drastic measures were taken to control venereal disease. Among the measures enforced was compulsory medical examination of prostitutes twice weekly. Serologic tests were made every two months. Desneux[122] found that during weeks of repeated and careful examinations signs of syphilis were uncovered. Finally a positive serologic reaction would reveal occult primary syphilis. From June 1940 to January 1946, 565 prostitutes under observation were found to have syphilis; 62 had primary symptoms; 84 had secondary syphilis; 419 were clinically free of signs. Of the latter, 249 had various stages of latent syphilis; the remaining 170 had no signs and disclaimed a history of syphilis and the disease was detected only by serologic tests. Of these 170 patients 50 per cent apparently had occult syphilis. The majority of the 170 patients had been under surveillance for three years or more. The author thinks that more than one battery of biologic tests is necessary to detect syphilis and that sometimes five batteries may be necessary to complete diagnosis. Desneux concludes that clinical primary syphilis escapes detection in a great proportion of cases even after a more thorough examination. Under the best controlled conditions this occurred in no less than 50 per cent of the cases. Judging from the article and its lack of details, one wonders just what is referred to as a "most thorough examination."

122. Desneux, J.: Detection of Primary Cases of Syphilis Without Clinical Symptoms by Serological Tests Only, Brit. J. Dermat. & Syph. **60**:235-238 (July-Aug.) 1948.

Extragenital Chancres.—Tucker and Mulherin [123] reviewed a series of 219 cases of extragenital chancres (160 from the syphilis clinic of the Johns Hopkins Hospital; 37 from the private practice of Moore and associates, and 22 from the Harriet Lane Home for Invalid Children) for the purpose of elucidating the sociologic, racial and clinical features found in patients with extragenital chancres and to point out some of the sources of diagnostic confusion. The highest incidence of extragenital chancres occurred in the age group between 20 and 40 years. A preponderance of extragenital chancres occurred in females and in the white race. The majority of extragenital chancres were located on the lip or adjacent to the buccal cavity. Multiple extragenital chancres occurred in 9.4 per cent. Some of the lesions occurred in patients who definitely had had no sexual contacts. The very low percentage of patients for whom the disease was diagnosed in the seronegative stage shows that the index of suspicion of syphilis in case of lesions located outside the genitalia was indeed low. This indicates the need for the physician to consider more frequently the possibility of extragenital chancre on any part of the body where there is an indolent, indurated lesion, especially if it is accompanied with unilateral adenopathy.

Myelogram in Syphilis.—Bertellotti and Biagini [124] studied myelograms of 30 patients with either primary or secondary syphilis. The material was obtained by sternal puncture. The majority of the patients were between the ages of 20 and 30 years. The myelogram was normal for all patients who were in good general condition, whereas it indicated parenchymal hyperplasia in patients in poor general condition. The functional study of the sternal marrow showed a defect in the maturation of the cells, which in some cases was inhibited and in other cases accelerated. The curves of maturation did not follow typical diagrams. Hypereosinophilia was frequent in myelograms of patients who had had no treatment as well as in those taken from patients in the course of the Herxheimer reaction, of erythema of the ninth day and of arsenical erythroderma. The authors believe that the Herxheimer reaction, erythema and erythroderma are allergic reactions to syphilis, treponeme toxins and arsenic, respectively.

Acute Syphilitic Nephrosis.—Cook and Warshawsky [125] report a case of syphilitic nephrosis in a 23 year old Negro man with secondary

123. Tucker, H. A., and Mulherin, J. L.: Extragenital Chancres: A Survey of Two Hundred and Nineteen Cases, Am. J. Syph., Gonor. & Ven. Dis. **32**:345-364 (July) 1948.

124. Bertellotti, L., and Biagini, E.: Contributo alla conoscenza del mielogramma nella lue recente, Arch. ital. dermat., sif. **21**:13-38, 1948.

125. Cook, H. D., and Warshawsky, H.: Acute Syphilitic Nephrosis: Case Report, Am. Pract. **3**:129-130 (Oct.) 1948.

syphilis. About twenty four hours after the patient first noticed the appearance of the secondary lesions, swelling of the ankles, face and hands developed, accompanied with oliguria. The patient was afebrile, and results of renal function tests were within normal limits. The urinalysis revealed a positive reaction for albumin and a few fine granular casts. The serum cholesterol was elevated (700 mg. per hundred cubic centimeters) and the Wassermann and Kahn reactions of the blood were strongly positive. About eight days after the onset of the edema a spontaneous diuresis developed; it lasted for three days. The edema subsided, and fourteen days after the onset of the edema the urine became negative for albumin. Treatment was instituted after the edema subsided. The patient received 50,000 units of penicillin every three hours for a total of 6,000,000 units. There was no Herxheimer reaction, and the urine remained negative for albumin. There has not been a recurrence of the edema. The serum cholesterol fell slowly and remained at 320 mg. per hundred cubic centimeters at the completion of penicillin therapy. This case tends to support previous reports in the literature [126] of cases of syphilitic nephrosis which cleared up before the institution of specific therapy.

Electrocardiographic Changes in Early Syphilis.—Steiger and Edeiken [127] observed abnormalities of the T wave in the electrocardiograms of 42.5 per cent of a small series of patients with early syphilis. A control group of only 8 nonsyphilitic patients receiving penicillin showed no abnormality of the electrocardiogram. The changes appeared to be transient in most cases, but in a few they persisted over a period of several months. Apparently penicillin is not responsible for these changes.

Osteomyelitis of the Skull in Early Syphilis.—Thompson and his colleagues [128] report their observations on 2 patients with signs and symptoms of secondary syphilis with osseous involvement of the skull and long bones at the site of orthopedic injuries. The first case was that of a 27 year old white soldier who sustained injuries to the head, spine and arm in an automobile accident. Four months later a constant dull headache developed, which was severe over the frontal region but was also localized over the parietal region. Stereoscopic roentgeno-

126. Patton, E. W., and Corlette, M. B.: Three Cases of Acute Syphilitic Nephrosis in Adults, Ann. Int. Med. **14**:1975-1980 (May) 1941.

127. Steiger, H. P., and Edeiken, J.: Further Observations of the Electrocardiographic Changes in Early Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **32**: 391-398 (July) 1948.

128. Thompson, R. G.; Leedham, C. L., and Hailey, H.: Osteomyelitis of the Skull in Early Syphilis—Report of Two Cases Probably Influenced by Trauma, Am. J. Syph., Gonor. & Ven. Dis. **33**:34-42 (Jan.) 1949.

grams of the skull revealed several eroded areas in the frontal bone which involved both the inner and the outer tables. The bone lesions were predominantly destructive. The patient's headache continued to grow worse, and a maculopapular nonpruritic rash appeared over the abdomen, back and arms. There was a generalized nontender lymphadenopathy. The Kahn and Wassermann reactions were both positive, the former in a titer of 240 Kahn units. Dark field examinations of the skin lesions did not disclose spirochetes. Spinal fluid examination was reported as showing 1 cell, a negative Pandy reaction, a Wassermann reaction negative in 0.5 cc. and positive in 1.0 cc., colloidal gold curve 1222100000 and total protein 28 mg. per hundred cubic centimeters. Repeated roentgen examinations showed progression of the osteolytic lesions in the skull and also a mild periostitis of the right humerus. The Kahn titer had risen to 400 units. A diagnosis of secondary syphilis with early osteomyelitis of the skull and periostitis of the right humerus was made. The patient received a total of 9,000,000 units of aqueous penicillin administered every three hours for a period of ten days. The patient did not have a febrile reaction, but the headache lessened in intensity and two weeks after therapy it completely disappeared. The osteomyelitis of the skull improved slowly.

The second case was that of a 26 year old white man who had suffered a fractured skull in 1938. In December 1947 he was admitted to the hospital because of pains in the legs of three days' duration. The Kahn and Wassermann reactions were reported positive. Roentgenograms of the legs revealed a periostitis involving the distal half of each tibia, and films of the skull revealed a punched-out area in the right parietal bone. The Kahn reaction was reported positive (400 units). Examinations of the spinal fluid showed no cells, a 1 plus reaction for globulin, the Wassermann reaction positive in 1.0 cc., colloidal gold curve 1122200000 and total protein of 50 mg. per hundred cubic centimeters. A diagnosis of syphilitic osteomyelitis of the skull and periostitis of both tibias was made. The patient received 100,000 units of penicillin every three hours for a total of 8,000,000 units. Seventy-two hours after the first dose of penicillin the headache and malaise had disappeared and the aching in the lower legs had noticeably diminished. Four months after completion of treatment the periostitis of the tibias had completely healed and the defect in the parietal bone was filling in.

The authors feel that it is probable that the head injuries suffered at the time of the accidents and prior to infection with syphilis were instrumental in determining the location of the bone lesions and their subsequent destructive course. Both patients responded to penicillin therapy with a disappearance of clinical signs and symptoms and healing of the osteolytic skull lesions.

RELAPSE AND REINFECTION

Not much has been published, aside from the papers dealing with treatment, on the matter of relapse and reinfection during the period covered by this review. The following reports on so-called reinfection are representative of the type of situation rather frequently noted after penicillin therapy.

Reinfection following adequately treated early syphilis is known to occur, but it is rare following late syphilis subsequently adequately treated. However, a case of primary syphilis developing in a patient with cardiovascular syphilis was reported by Thomas in 1945. Because of the rarity of such cases Peabody and Webster [129] present 2 case reports of dark field–positive early infectious syphilis (primary and secondary) occurring in patients previously adequately treated for cardiovascular syphilis and, in 1 case, simultaneous asymptomatic neurosyphilis. It is of interest to note that the serologic reactions of both patients had become negative after the initial antisyphilitic therapy. Four to five years passed before reinfection occurred. Reynolds and Moore have suggested that the phenomenon may be due to cure of the original infection and the gradual disappearance of whatever immunity it may have engendered.

A man with dark field–positive, seropositive primary syphilis was treated by Bolgert and his co-workers [130] with 15,000,000 units of penicillin from Nov. 25 to Dec. 8, 1947. The lesion healed, and the serologic tests were negative on December 22. Negative reactions were obtained on Dec. 29, 1947 and Jan. 5 and 12, 1948. On January 8, a dark field–positive chancre developed on the prepuce (not site of original lesion) and regional adenopathy. The serologic tests were negative on January 12 and positive on January 26 and February 8. The only sexual contacts, about Christmas and January 7, were with one woman who on examination showed secondary syphilis. This was the first reinfection after massive doses of penicillin seen by the authors.

LATE SYPHILIS

Benign Late Syphilis.—That syphilis may remain dormant for decades is sometimes not appreciated. Wiggall and Hahn [131] reviewed the histories of 1,872 patients at Johns Hopkins Hospital with benign

129. Peabody, G. E., and Webster, B.: Reinfection Following Late Syphilis, J. Ven. Dis. Inform. **29**:337-339 (Nov.) 1948.

130. Bolgert, M.; Lévy, G., and Goujeon, J.: Premier cas de réinfection syphilitique après pénicillinothérapie massive, Bull. Soc. franç. de dermat. et syph. **55**:116-117 (March-April) 1948.

131. Wiggall, R. H., and Hahn, R. D.: Benign Late Gummatous Syphilis Occurring More Than Forty Years After Infection, Am. J. Syph., Gonor. & Ven. Dis. **33**:270-273 (May) 1949.

late syphilis and found 3 with periods of forty-three, forty-seven and sixty years between infection and symptoms. They noted that a number of patients over 65 years of age with gummas were unable to date their infection, and conclude that long periods of apparent perfect symbiosis between host and parasite may not be as unusual as sparse reports in the literature indicate.

Témime and his group [132] report a rare form of late syphilis which is interesting by virtue of its histologic and allergenic anomaly and also the difficulty in distinguishing this lesion from vegetative tuberculosis or pyodermic lesions of the skin. The patient presented a vegetating papillomatous tertiary syphilitic lesion occurring on the upper lip in a 44 year old white male patient. The onset followed a traumatic injury of the lip after shaving, and the lesion was of two years' duration. Associated with the verrucous growth was a sclerotic glossitis and leukoplakia of the buccal mucosa. The serologic test elicited a strongly positive reaction.

Kierland and Underwood [133] described a case of gumma of the sternocleidomastoid muscle in a 61 year old man. The serologic reaction for syphilis was positive, 320 Kahn units. In spite of the positive serologic reaction, the patient was operated on and the anterior two thirds of the muscle excised. Three months later when the patient returned for reexamination there was no evidence of recurrence. The Kahn reaction was positive, 512 units. Reexamination of the tissue showed changes consistent with gumma of the muscle. The patient returned home to receive antisyphilitic treatment from his physician.

Gumma of the Lung.—Bradley [134] reports a case of gumma of the lung in a 39 year old Negro. The case reported is unique in that the disease was suspected clinically and confirmed histologically in a living patient by examination of pulmonary tissue removed by lobectomy. The patient disclaimed lesions of early syphilis. His serologic reactions for syphilis were strongly positive. In a fifteen day period he received a total of 20,800,000 units of penicillin, 200 mg. of bismuth compound weekly and 45 drops of potassium iodide by mouth daily. Five days after completion of this therapy excision of the lower lobe of the left lung was performed, and an uneventful recovery followed. Histologic study of the specimen revealed a multilocular lesion composed of necrotic tissue and lung parenchyma. The necrotic areas were not caseous. The fibrous tissue was cellular, and an occasional multinucleated giant

132. Témime, P.; Robattu, J., and Amaluric, R.: La syphilis tertiare végétante de la peau, Semaine d. hôp. Paris **24**:2223-2227 (Sept. 14) 1948.

133. Kierland, R. R., and Underwood, L. J.: Gumma of Skeletal Muscle: Report of Case, Am. J. Syph., Gonor. & Ven. Dis. **32**:491-493 (Sept.) 1948.

134. Bradley, D. F.: Gumma of the Lung: Report of a Case, Arch. Dermat. & Syph. **58**:444-450 (Oct.) 1948.

cell was seen. The alveoli had swollen endothelial cells, and some had accumulations of large foamy macrophages. In addition, there was considerable round cell infiltration, consisting mostly of plasma cells. Some of these collections were around blood vessels. Certain blood vessels showed endothelial proliferation. A Levaditi stain failed to reveal the unequivocal presence of spirochetes. The pathologic picture was compatible with gumma of the lung. The serologic tests for syphilis remained strongly positive six months after the penicillin therapy and the lobectomy.

Late Syphilis of the Thyroid Gland.—Csonka [135] reports the case of a 55 year old woman who was studied at St. Mary's Hospital, London, because of a painless swelling of the neck, some breathlessness, huskiness of the voice and, later, a punched-out ulcer over the isthmus of the thyroid gland. The results of the Wassermann and Kahn tests of the blood were strongly positive, and so was the luetin skin test. A diagnosis of late syphilitic thyroiditis was made, and therapy was initiated with weekly intramuscular injections of a bismuth preparation. After two injections the swelling decreased, and after the third injection the voice returned to normal. The patient was then given 4,800,000 units of penicillin in oil and wax in eight daily injections. At the end of this time the swelling in the neck disappeared, the ulcer healed and a deep scar was the only visible sign.

BONE AND JOINT SYPHILIS

In a monograph of 419 pages Sundt [136] reviews the subject of arthrosyphilis on the basis of the literature and his own 49 patients observed at Kysthospitalet, Stavern, Norway. Syphilitic involvements of joints has been known for a long time, even perhaps in prehistoric time. During the period 1892 to 1944 there were 49 cases observed in this Norwegian institution. Of these, the diagnosis was established with certainty in 44 cases and with probability in 5. In three fourths of the cases the disease was undoubtedly tardive congenital syphilis. The patients were 21 men and 28 women. There has been much controversy regarding the status of arthrosyphilis. Sundt gives detailed arguments in support of the syphilitic nature of the process in its various phases. Numerous studies, including sedimentation rate, cytologic, roentgenologic, histologic and serologic, may yield completely negative results. The therapeutic reaction is said to be most important in diagnosis, but it is noted that arthrosyphilis may be highly resistant to "specific" therapy, necessitating interchange of remedies (arsenic, bis-

135. Csonka, G. W.: Late Syphilis of the Thyroid Gland, M. Illust. **3**:26-29 (Jan.) 1949.

136. Sundt, H.: Arthro-syphilis congenita tardiva et acquisita et arthrometasyphilis, Acta dermat.-venereol. (supp. 20) **28**:1-419, 1948.

muth and iodides) and large doses. In refractory cases gold therapy is needed. Twenty-seven of the patients were followed from three to forty years after treatment (over half of them more than twenty years). Twenty-two were deemed to have definite arthrosyphilis, and, of these, 19 had been free from recurrence and had been able to work. Two of the remaining 3 had received incomplete treatment, and 1 had been given none. There was a mild recurrence in 1 of these 3 incompletely treated patients, but the other 2 remained free from relapse. There was mixed infection in the other 5 of 27 patients adequately followed. Two of these had no recurrence twelve and twenty years respectively after therapy. Whether trauma plays a role in many of the cases is questionable.

In connection with osseous syphilis we cite the experience of Oosthuizen,[137] of the Pretoria General Hospital, regarding the roentgen appearance in a number of cases of proved yaws affecting long, short and flat bones. The roentgenologic features of yaws may be classified as (1) periosteal reactions, with laying down of new bone and periosteal thickening; (2) erosion, which sometimes has a "punched-out" appearance; (3) cystlike changes, in the skull in particular; (4) sclerosis, usually developing side by side with the erosion; (5) sequestrum formation, especially common in the hands and feet; (6) abnormality in contour; (7) joint involvement, and (8) soft tissue swelling. Most of these changes are well illustrated by excellent photographs.

CONGENITAL SYPHILIS

Congenital Syphilis and Rickets.—The cases of coexisting rickets and congenital syphilis examined by Bromer and Harvey[138] at the Children's Hospital, Philadelphia, all occurred in early infancy. In no case could the authors determine the presence of the characteristic changes of "osteochondritis luetica" in the metaphysial and epiphysial areas of the long bones. The periosteal involvement in the two conditions is so similar that differentiation in the roentgenogram is impossible.

Third Generation Syphilis.—Third generation syphilis, an interesting although relatively unimportant phase of syphilology, still commands some attention, as exemplified by the reports of Landtman[139] and of Hollström.[140]

137. Oosthuizen, S. F.: Yaws, Brit. J. Radiol. **22**:276-279 (May) 1949.

138. Bromer, R. S., and Harvey, R. M.: The Roentgen Diagnosis of Rickets Associated with Other Skeletal Diseases of Infants and Children, Radiology **51**:1-10 (July) 1948.

139. Landtman, B.: Case of Congenital Syphilis in the Second Generation, Nord. med. (Finska läk.-sällsk. handl.) **27**:1705-1707 (Aug. 31) 1945.

140. Hollström, E.: A Seroresistant Case of Third Generation Syphilis with Liquor Changes, Acta dermat-venereol. **28**:1-6, 1948.

CARDIOVASCULAR SYPHILIS

In the area of cardiovascular syphilis several valuable reviews (Moore,[141] Fleming[142] and Briggs and Karstens[143]) have appeared and are presented in some detail. In connection with this category of syphilis reference should be given to the electrocardiographic changes in early syphilis reported by Steiger and Edeiken,[127] previously referred to.

According to Moore,[141] the past decade has seen few or no important advances in the diagnosis and treatment of cardiovascular syphilis. A survey of necropsy material in five large medical centers to determine whether syphilis of the aorta is more or less frequent now than during previous decades revealed completely conflicting results. However, in spite of the inadequacy of the conflicting data, it is reasonably established that the "adequate" treatment of early syphilis affords partial, if not complete, protection against the subsequent clinical development of clinically recognizable cardiovascular syphilis. Kemp and Cochems in 1937 studied 743 patients who had received varying amounts of treatment for early syphilis and who had thereafter been followed for ten or more years. The incidence of clinically detectable cardiovascular syphilis was 27.6 per cent for persons receiving little or no treatment for early syphilis and 13.9 per cent when some but "inadequate" treatment had been given; no cases were observed among 114 patients who had received "adequate" treatment. These data are confirmed by Thompson, Comeau and White.

Maynard and Lingg likewise agree that cardiovascular syphilis developed five times as frequently (in their series of 600 syphilitic patients) among those receiving no previous treatment or practically none as among those to whom "adequate" courses of metal chemotherapy had been given. The incidence of syphilitic heart disease decreased as the amount of antisyphilitic therapy increased. There is some evidence, too, that the "adequate" metal chemotherapy of late latent syphilis may prevent the development of cardiovascular syphilis. Granting the probability of this prophylactic effect of treatment, it is reasonable to anticipate that the campaign to control syphilis which has brought literally millions of patients with early and late syphilis under treatment in this country in the past twelve years (Heller) will be reflected in a great decline in the incidence of cardiovascular syphilis

141. Moore, J. E.: Cardiovascular Syphilis—A Summary of Recent Information with Special Reference to Treatment with Penicillin, Am. J. Syph., Gonor. & Ven. Dis. **33**:43-55 (Jan.) 1949.

142. Fleming, W. L.: Cardiovascular Syphilis, Bull. Ven. Dis., Mass. Dept. Pub. Health **11**:1-4 (July) 1948.

143. Briggs, J. F., and Karstens, A.: Syphilitic Heart Disease, Dis. of Chest **15**:168-173 (Feb.) 1949.

in the next quarter century. The influence of penicillin in preventing the subsequent development of cardiovascular syphilis will, of course, be undeterminable for two or more decades in the future.

It has been repeatedly pointed out by many investigators that the best hope for therapeutic success in cardiovascular syphilis lies largely in the recognition of aortic involvement before the development of valvular insufficiency or saccular aneurysm. Necropsy studies for many medical centers confirmed the fact that from 80 to 90 per cent of patients with long-standing syphilitic infections inadequately treated during the early stages show pathologic evidence of syphilitic aortitis. It is a reasonable presumption, therefore, that in any patient who has had syphilis ten or more years, microscopic lesions of the aortic wall due to syphilitic infection are actually present. The majority of patients with long-standing syphilis may therefore be assumed to have subclinical aortitis unrecognizable by symptoms, physical signs or roentgenologic evidence. The important question is the number of these in whom clinical evidence sufficient to justify the diagnosis develops. Here there are wide conflicts of opinion. Such careful observers as Wilson, Morgan, Kampmeier and many others are convinced that there are no characteristic symptoms or physical signs permitting the diagnosis of syphilitic aortitis uncomplicated by insufficiency or aneurysm. The Johns Hopkins group agree that uncomplicated syphilitic aortitis is often an asymptomatic disease, but they feel that the extent to which this is true varies with two factors: (*a*) the extent of pathologic damage to the aorta, and (*b*) the care devoted to history taking and to physical and laboratory examinations of the patient. The available evidence indicates that in the hands of an experienced and duly suspicious observer the clinical diagnosis of uncomplicated aortitis can be made successfully and accurately, as demonstrated by subsequent observations at necropsy, for a fair proportion of patients with this condition but that the diagnosis rests on a combined evaluation of relatively insignificant symptoms, physical signs and highly expert roentgenologic study.

Wile and Snow emphasize that both aortic insufficiency and saccular aneurysm may be entirely symptomless conditions discovered only on routine physical examination. Among 2,718 syphilitic patients examined at the Cornell Clinic from 1936 to 1941, McDermott's group found the incidence of syphilitic aortic insufficiency without aneurysm to be 3.4 per cent. Half of these patients with aortic regurgitation disclaimed any symptoms of cardiac insufficiency at the time of diagnosis. Only one third of them sought medical care because of symptoms referable to the heart. The aortic width, as judged from appropriate roentgenologic examinations, was normal in 43 per cent of these patients with aortic insufficiency. Twenty-eight of the asymptomatic patients

were followed for more than two years, during which time only 2 died of heart disease and only 2 others showed symptoms.

Electrocardiographic studies in syphilitic aortitis are not characteristic except where there is involvement of one or both coronary ostiums. One of the extraordinary mysteries of syphilis for which no reasonable explanation has as yet been advanced is the almost complete absence of clinical or autopsy evidence of syphilitic aortitis or other forms of syphilitic cardiac disease in patients with the congental infection, as contrasted to its almost uniform presence in patients with the late acquired disease. Hinrichsen describes two definite types of myocardial lesions in congenital syphilis, interstitial and nodular myocarditis, in each of which spirochetes can be demonstrated.

Moore briefly reviews the results of metal chemotherapy in cardiovascular syphilis. He points out that nearly forty years after the first introduction of salvarsan by Ehrlich and the initiation of effective metal chemotherapy, there are available only three comparable and reliable studies of the effect of antisyphilitic therapy in cardiovascular syphilis. Grant's data, based on 171 cases of aortic regurgitation followed for ten years or until death, showed no difference in the average duration of life in the two groups: eighty-nine months for the treated group and eighty-seven months for the untreated group.

Moore discusses penicillin in the treatment of cardiovascular syphilis. He states that the concept of "therapeutic paradox" has been exaggerated, and in his opinion there is no greater danger from it after treatment with penicillin than after treatment with arsenic and bismuth preparations. He states that the Herxheimer reaction is another and more serious matter. The focal reaction (increased flare in local lesions) with edema and cellular infiltration is important in cardiovascular syphilis. However, in 30 patients with cardiovascular syphilis treated with penicillin, there were 5 in whom a febrile Herxheimer reaction developed, but all 5 of these had associated neurosyphilis. No patient manifested cardiovascular symptoms unless such symptoms had not been previously present, nor were there any detectable changes in serial electrocardiograms, leukocyte counts or sedimentation rates. From this, Moore concludes that the risk of the Herxheimer reaction from penicillin in cardiovascular syphilis has been greatly exaggerated. Nevertheless, and until further evidence is forthcoming, the Syphilis Study Section of the National Institutes of Health remains noncommittal. They say: "In syphilitic aortitis with aortic regurgitation, saccular aneurysm, or obvious or masked coronary or myocardial disease, it may be advisable to withhold penicillin altogether, or at least until after heavy metal preparatory treatment has been given."

In a brief review of the subject of cardiovascular syphilis, Fleming [142] discusses the incidence, pathology, diagnosis and treatment of this phase

of the disease. He cites the pathologic studies of Langer, Warthin and Nickel, which actually show that 70 to 90 per cent of all patients with lesions of late syphilis demonstrated at autopsy have at least microscopic evidence of syphilitic involvement of their aortas. These studies have been interpreted as indicating that 70 to 90 per cent of all persons with late syphilis have aortitis. However, many of the autopsy diagnoses of aortitis are based on microscopic lesions which could not be expected to have influenced anatomic form or physiologic function sufficiently to permit clinical diagnosis. From the clinical standpoint, Bruusgaard, in a long term follow-up of 473 patients with untreated syphilis, found 10 per cent with clinical evidence of cardiovascular involvement. Turner, in his survey of more than 6,000 patients with late syphilis, found approximately 10 per cent with cardiovascular syphilis (5.3 per cent with uncomplicated aortitis, 1.2 per cent with aortic aneurysm, 2.7 per cent with aortic insufficiency and 0.7 per cent with various other types). According to White and Maher, about 5 to 10 per cent of all cases of clinically recognized heart disease are due to syphilis. Turner's study indicated that cardiovascular syphilis is twice as common in males as in females and definitely commoner in Negroes than in white persons. Rosahn's autopsy study on the outcome of untreated syphilis indicates that cardiovascular syphilis is the most frequent cause of death from acquired syphilis.

According to Fleming, syphilitic aortitis constitutes the basic pathologic lesion of all cardiovascular syphilis except the rare condition of syphilitic myocarditis. Syphilitic changes occur most commonly in the root and arch of the aorta and become rarer with distal progression in the aorta. Invasion of the aorta occurs during the period of early syphilis. The exact route of invasion is not known, but the organisms are thought to penetrate the aortic wall by way of the vasa vasorum and perivascular round cell infiltration is frequently found, particularly in the adventitia. Degeneration occurs in the media of the aorta, resulting in destruction of elastic tissue with connective tissue replacement. If the process is minimal, no anatomic or physiologic alterations occur. If the process is severer but fairly evenly distributed and does not involve the aortic ring, only diffuse dilatation with some elongation occurs (uncomplicated aortitis). If focal damage is severe, aneurysm formation may occur. Involvement of the very root of the aorta may lead to dilatation of the aortic ring and aortic insufficiency. Involvement of the aortic ring and base of the aorta may also lead to narrowing of the mouths of the coronary arteries, resulting in myocardial ischemia and myocardial failure. The diagnosis of uncomplicated syphilitic aortitis has led to a great deal of discussion. Some authorities have taken the position that it is practically an undiagnosable condition, while Moore and his group have taken a more optimistic point of view and have proposed

seven diagnostic criteria, the presence of any three of which would permit the diagnosis for a patient known to have late syphilis and without signs of mitral disease.

Syphilitic aortic insufficiency has to be differentiated from aortic insufficiency due to other causes and particularly from rheumatic aortic insufficiency. The syphilitic type is almost always pure insufficiency, whereas the rheumatic lesion is almost always a combination of stenosis and insufficiency associated with a mitral lesion. This means that in some cases rheumatic and syphilitic lesions can be distinguished on the basis of physical signs, but the frequent occurrence of aortic systolic murmurs and of Austin Flint murmurs makes the differential diagnosis on physical finding alone sometimes impossible.

The diagnosis of aneurysm is best made by roentgenographic or fluoroscopic examination. Padget, Kemp and Cochems and Rosahn have all shown that adequate treatment of early syphilis practically eliminates cardiovascular syphilis. Aims of treatment should be the relief of distressing symptoms, if present, and the prolongation of life. Treatment should be so designed as to give the maximum chance of benefit with minimum risk. Already existing damage cannot be repaired, but further damage may be prevented. Treatment should be based on careful clinical evaluation of the patient and therapy individualized. Aortitis calls for permanent limitation of physical activity. Cardiac decompensation calls for measures designed to restore compensation rather than specific antisyphilitic therapy. Three dangers to be avoided in specific therapy are (1) sudden circulatory failure and death (due mainly to arsenical drugs); (2) therapeutic shock or Jarisch-Herxheimer reaction, and (3) therapeutic paradox. Fleming feels that such dangers can best be avoided by individualization of therapy, by institution of treatment with slow-acting drugs, by avoiding specific treatment during congestive failure and by particular care in treating patients with angina. Fleming's experience in treatment of cardiovascular syphilis has been confined mainly to the arsenic-bismuth system. Treatment consists of administration of 0.2 Gm. of bismuth subsalicylate weekly for a period of twelve weeks. A saturated solution of potassium iodide (30 drops three times a day) may be given along with the bismuth. In uncomplicated aortitis oxophenarsine hydrochloride (mapharsen®) in a dose of 0.01 Gm. is started after the preliminary twelve weeks' course of bismuth. The amount of oxophenarsine hydrochloride is gradually increased to a maximum dose of 0.03 to 0.04 Gm. Alternate courses of oxophenarsine hydrochloride and bismuth subsalicylate are given over eight week periods for about two years. In aortic insufficiency and aneurysm careful consideration is given each case before deciding on whether arsenic should be given. The treatment of cardiovascular syphilis with penicillin, while under experimental investigation, cannot

be evaluated as to its effectiveness and also its dangers until more time has elapsed. It is already clear from experience with penicillin that the danger of Herxheimer reactions has been exaggerated in the past and that perhaps some of the apparent Herxheimer reactions were really due to the toxicity of the arsenical. There have been a few suggestive dangerous Herxheimer reactions or therapeutic paradoxes, but not completely clearcut, with penicillin therapy. However, caution in initiating treatment is still in order if penicillin is to be used. If there is no clearcut reason for haste in getting a treatment effect, such as coexisting dementia paralytica, it is probably wisest to defer penicillin until after the patient has received bismuth therapy for eight to twelve weeks.

Briggs and Karstens [148] state that syphilitic heart disease is a misnomer, for the basic lesion in syphilitic heart disease is aortitis. This, in turn, consists in a perivascular lymphocytic infiltration of the vasa vasorum in response to the invasion of the spirochete. Depending on the extent and the degree of this infection within the aorta, the basic lesion of aortitis may be complicated by aortic insufficiency, coronary ostial closure or aneurysm formation. The authors selected a group of 161 cases of proved syphilitic aortitis from a series of 10,000 cases coming to necropsy. In 96 of these cases the Wassermann reaction of the blood was positive. In 49 of the 96, Wassermann reactions of the spinal fluid were indeterminate—not completely positive—in 29 positive and in 17 negative. In 45 of the 161 cases the Wassermann reaction of the blood was indeterminate, and in 19 it was negative. In this group of cases of syphilitic aortitis coronary ostial closure was rather common. It involved the right coronary artery in 69 cases, with complete closure of the ostia in 8. In 50 of the 69 cases the left coronary artery was somewhat involved but to less extent. Valvulitis occurred in 85 of the cases; of these, there was valvulitis alone without aortic insufficiency in 32 and in 53 aortic insufficiency was present. In 18 cases there were miscellaneous complications, such as rheumatic heart disease, auricular fibrillation, hypertension and subacute bacterial endocarditis. Aortic aneurysm was noted in 19 cases; in 6 of these cases the aneurysm ruptured, producing cardiac tamponade in 3, bleeding into the pleural space in 2 and retroperitoneal bleeding in 1. Of the entire series of cases, syphilitic heart disease was the major cause of death in 41; in 96 the syphilitic artery disease had no connection whatsoever with the cause of death, and in 24 it was a contributing cause of death. Rheumatic valve defects were present in 14 cases; the aortic valve was involved in 5, the mitral valve in 8 and the tricuspid valve in 1. Bacterial endocarditis occurred in 5 cases. It was implanted on a previous rheumatic valve defect in 4, and in only 1 was it on a syphilitic defect. Auricular fibrillation occurred in 8 cases, and in all of these some other complicating

cardiac disease was present, such as rheumatic heart disease or hypertension. Myocardial infarction as a result of closure of the coronary ostia occurred in 3 of the cases; in 2 of these, death was sudden.

Schwedel and Simon [144] examined 595 men with syphilis and 786 controls for auscultatory and roentgenographic findings to determine the incidence of aortic dilatation, aortic insufficiency and a combination of aortic dilatation plus aortic systolic murmur and/or accentuation of the second aortic sound. The average incidence of dilated aorta was 4.2 per cent in the controls and 18 per cent in the syphilitic group. Auscultatory findings were three times as frequent in the syphilitic group without aortic dilatation and twice as frequent when the aorta was dilated. Isolated aortic insufficiency was present in 7.2 per cent. Criteria for the diagnosis of syphilitic aortitis are suggested, consisting in the presence of a dilated aorta combined with significant auscultatory findings. The presence of a dilated aorta in persons below the age of 40 years with syphilis in the absence of aortic insufficiency, plus aortic systolic murmur or accentuation of the aortic second sound, is sufficiently frequent to warrant the presumptive diagnosis of syphilitic aortitis.

Aneurysm of the Abdominal Aorta.—Foord [145] reviews briefly the pathogenesis, manifestations and sequelae of aneurysms of the abdominal aorta, of which syphilis causes a predominant number. He reports 3 illustrative cases. Aneurysms of syphilitic origin occur most frequently in the upper portion of the abdominal aorta, that is, above the renal arteries, and those due to arteriosclerosis in the lower portion, especially near the bifurcation. Pathologically the changes produced by the two diseases are reasonably distinct. Syphilis causes primarily a mesarteritis with patchy lymphocytic infiltration about the vasa vasorum as they pass through the adventitia and media. In contrast, atherosclerosis produces gradual hyalinization of the media and degenerative intimal changes with thickening and plaque formation. The syphilitic changes are moderately rapid, producing marked scarring and early dilation, whereas those due to atherosclerosis are gradual but nonetheless progressive. In discussing the differential diagnosis, the author states that because of the common cause, it may be impossible to exclude tabes dorsalis with gastric crises, except for the absence of physical signs of aneurysm, unless possibly neurologic signs seem to predominate.

Aneurysm of the Coronary Arteries.—Scott [146] suggests that aneurysms of the coronary arteries be considered as localized or diffuse

144. Schwedel, J. B., and Simon, K.: Cardiovascular Syphilis in Young White Males, Am. Heart J. **37**:675 (April) 1949.

145. Foord, E.: Aneurysms of the Abdominal Aorta, Yale J. Biol. & Med. **20**:441-448 (May) 1948.

146. Scott, D. H.: Aneurysm of Coronary Arteries, Am. Heart J. **36**:403-421 (Sept.) 1948.

and that the localized lesions be further classified into four main groups: congenital, mycotic-embolic, syphilitic and arteriosclerotic. All diffuse aneurysms of the coronary arteries appear to be on a congenital basis. A total of 47 cases of localized aneurysm have been reported since the first report, in 1812; the lesions may be divided into 15 congenital, 12 mycotic-embolic, 6 syphilitic, 6 arteriosclerotic, 4 of other types and 4 unclassified. The common complications of the condition are rupture, thrombosis and associated myocardial disease. When a localized aneurysm occurs, the left coronary artery is the more frequently involved and the condition is usually single. In a diffuse aneurysm, the right coronary artery is more commonly affected. There are no pathognomonic clinical findings. Men are much more frequently affected than women. One case of coronary aneurysm in a man aged 84 is reported; there were no cardiac complaints during life, and at autopsy there was observed an anomalous coronary circulation with multiple aneurysms, the largest of which measured 10 by 8.0 by 8.0 cm. The case is of particular interest as an illustration of the extent to which an abnormality can be present in the heart without causing symptoms.

Calcification of Ascending Aorta.—Reporting from the Department of Radiology and Physical Therapy, University of Minnesota, Leighton [147] presents material to confirm the previously noted frequent association between syphilitic aortitis and calcification of the ascending aorta. The material was divided and reported in three groups. The first group consists of cases of syphilitic aortitis proved at autopsy in which roentgenograms of the chest were available. Leighton had 20 cases in this category. In 11 of these there was calcification. In 2 of the 11, aneurysm was present; in 2 other cases there was aneurysm without calcification. Therefore, in 9 of 18 cases, or 50 per cent of the cases of aortitis without aneurysm proved at autopsy, there was calcification in the ascending aorta. Of the 39 cases in the second group, in which a clinical diagnosis of syphilitic aortitis was made, calcification was shown in 21 but in 4 the lesions were considered aneurysms. Omission of these left 17 cases, or 43 per cent, with calcification. Of the total number of patients (39) 66 per cent had positive Wassermann reactions. Group 3 was composed of cases in which calcification of the ascending aorta was shown on routine posteroanterior roentgenograms of the chest. In 13 of these, or 62 per cent, the calcification was associated with a positive Wassermann reaction; in 4 of the 13, or 30 per cent, there were other findings warranting a clinical diagnosis of syphilitic aortitis, and suggestive evidence was present in 8 cases. Therefore, 12 of 13 patients (92 per cent) with a positive Wassermann reaction and calcification of the ascending aorta had definite or probable syphilitic aortitis.

147. Leighton, R. S.: Calcification of the Ascending Aorta as a Sign of Syphilitic Aortitis, Radiology **51**:257-259 (Aug.) 1948.

Miscellaneous Manifestations of Cardiovascular Syphilis.—Mullins and his colleagues [148] report a single case of gumma of the aortic ring in a 28 year old Negro soldier. The patient died of acute myocardial failure secondary to rupture of the left and middle leaflets of the aortic valve superimposed on syphilitic aortic valvulitis with insufficiency. The patient died about eighteen months after the onset of a primary infection. Beginning in September 1943 he had received a total of thirty to thirty-five injections (two a week) for primary syphilis. Autopsy revealed the left and middle leaflets of the aortic valve destroyed and replaced by necrotic granulation tissue, an aneurysmal dilatation of the ascending aorta and narrowing of the ostiums of the coronary arteries. Microscopic examination revealed a gummatous infiltration of the aortic ring. Sections of the aortic ring and valve stained by Levaditi's technic revealed T. pallidum.

After an interesting historical survey and review of the pertinent modern literature, Moynahan [149] presents a case of gangrene of the toes in a 31 year old white man with a syphilitic infection of undetermined type and duration. Although there are no pathognomonic signs of peripheral vascular syphilis, Moynahan presents eight criteria which must be fulfilled to establish the absence of other causes of vascular disturbance and the presence of syphilis before such a diagnosis is made. In the final analysis the clinical diagnosis should be confirmed by the demonstration of spirochetes in the affected vessels.

OCULAR SYPHILIS

Interstitial Keratitis.—Graham and his co-workers [150] review the literature on interstitial keratitis, usually a late manifestation of congenital syphilis, and present a report of a study of 103 patients with the disease at the New York Eye and Ear Infirmary during the past twelve years. A recent decrease in the number of patients admitted has been noted, and since 1946 no new patients have been admitted. The authors attribute the decline to the institution of antepartum and premarital serologic tests, the effects of which would not have been noticed for a decade, since most cases of interstitial keratitis are observed in patients between the ages of 10 and 20 years. All patients were given

148. Mullins, D. F., Jr.; Marquis, H. H., and Schulze, W.: Syphilitic Gumma of the Aortic Ring and Left Ventricle, and Aneurysm of the Sinus of Valsalva, with Demonstration of Treponema Pallida, J. M. A. Georgia **37**:340-342 (Sept.) 1948.

149. Moynahan, E. J.: Gangrene of the Toes in Syphilis: Description of a Case with a Critical Review of the Literature, Brit. J. Ven. Dis. **24**:104-108 (Sept.) 1948.

150. Graham, T. N.; Romaine, H. H., and Rulison, R. H.: Syphilitic Interstitial Keratitis: Report of One Hundred and Three Cases, New York State J. Med. **48**:1916-1919 (Sept. 1) 1948.

routine therapy with a bismuth and an arsenical preparation over a period of two years, usually at intervals of one week. Since penicillin has become available it has been used in all cases, but routine therapy has also been employed. The authors feel that patients with a condition with such severe consequences as interstitial keratitis should be given therapy which has proved to be effective over a period of years. They recommend, therefore, that all patients with interstitial keratitis receive 6,000,000 units of penicillin in addition to routine therapy which has proved effective in the past, as well as local treatment. In a series of 49 adequately treated patients with interstitial keratitis excellent results were obtained in 53 per cent, in contrast to a final outcome of good vision in 12 per cent of inadequately treated patients. Results in adequately treated patients were good in 25 per cent, fair in 12 per cent and bad in 10 per cent. Of inadequately treated patients the outcome in 12 per cent was good, in 23 per cent fair and in 10 per cent bad. The incidence of recurrence in the entire group was approximately 30 per cent. Those who had adequate early treatment showed the least tendency toward recurrence, and those who had sporadic or no treatment showed the greatest tendency toward recurrence. The authors advocate close cooperation between the ophthalmologist and the syphilologist in treating patients with all forms of ocular syphilis.

Weskamp,[151] of Rosario, Argentina (Universided Nacional del Litoral) contributes a carefully planned study of the histopathology of interstitial keratitis due to congenital syphilis. His paper is based on biopsy material obtained in seven keratectomies on 5 patients with syphilitic interstitial keratitis in various stages of the disease, ranging from a clinical course of twenty-five days to two years. Keratectomy is not an ideal means of investigation, since it does not permit examination of the entire thickness of the cornea, but, since it can be performed without fear of damage to the patient, it provides a useful means of studying syphilitic interstitial keratitis. The material removed by keratectomy was first subjected to a search for T. pallidum by Jahnel's method, but organisms were not found. Then for histologic examination the tissue was fixed in formaldehyde or Bouin's solution (twice in Ruffini's), embedded in paraffin and stained by routine methods. Weskamp classifies the parenchymal changes chronologically as (1) infiltration and edema; (2) cellular necrosis and vascularization; (3) atrophy of the parenchyma, and (4) organization of fibrous tissue; each is correlated with the biomicroscopic appearance. In the early stages between twenty-five and ninety days, marked changes of the epithelium occur. These are characterized by infiltration of an exudate

151. Weskamp, C.: Histopathology of Interstitial Keratitis Due to Congenital Syphilis, Am. J. Ophth. **32**:793-806 (June) 1949.

containing lymphocytes and erythrocytes which disarranges the orderly architecture of the epithelial cells. The epithelium is detached from the basement membrane in long stretches, and there may be vesicle formation due to the edema. The epithelium is formed by one or two rows of cells in those places where the exudate had decreased or disappeared. Bowman's membrane is not altered during this stage; it remains perfectly normal and stains evenly. The parenchyma is infiltrated by the same elements as the epithelium. The lymph spaces are enlarged and contain fine detritus. The lamellas appear to be edematous but not markedly altered. Their fibers seem often to be swollen, thus giving a homogenous appearance to the lamellas. In this stage the nuclei of the normal cells of the parenchyma are swollen and show karyokinetic changes. In the more advanced stages, the epithelium seems to be repaired, since it shows a normal or increased number of layers. Epithelial prongs are seen within the parenchyma. Bowman's membrane undergoes marked changes. In places it has disappeared, or is disrupted or has been reduced in thickness. The parenchyma shows vascularization. The vessels have their own walls and some of them present active blood currents; others have their lumens clogged as a consequence of degenerative processes of their walls. A few lymphocytes and histiocytes are observed in the most advanced stage of the disease. The lamellar tissue is sometimes replaced by scar tissue.

Optic Neuropathies.—In the Estelle Doheny Eye Foundation Lecture, Alan C. Woods,[152] of Johns Hopkins University, attempts to clarify the confusion in the etiologic diagnosis of diseases of the optic nerve. Although the whole range of optic neuropathies is covered, there is sufficient discussion of syphilitic optic atrophy, primary and secondary, to make this a fundamental source of orientation for any one who treats patients with this condition.

Statistical studies of the causes of blindness attribute 10 to 15 per cent of the cases to syphilis. On the basis of a total of 230,000 blind persons in the United States, there would be 23,000 to 34,500 with syphilitic blindness in this country. Ninety per cent of the cases of blindness caused by syphilis can be attributed, according to Klauder, Meyer and Gross,[153] to optic atrophy of acquired and congenital syphilis. These authors also cite figures from the literature which emphasize the magnitude of this problem. In addition, they touch on the pathogenesis of syphilitic primary optic atrophy. The principal sites of involvement are the intracranial portion of the optic nerves, the chiasm or both.

152. Woods, A. C.: Optic Neuropathies: A Simplified Classification and Outline for Etiologic Diagnosis, Am. J. Ophth. **31**:1053-1069 (Sept.) 1948.

153. Klauder, S. V.; Meyer, G. P., and Gross, B. A.: Syphilitic Primary Optic Atrophy as a Cause of Blindness: Importance of Early Diagnosis, Am. J. Syph., Gonor. & Ven. Dis. **32**:514-586 (Nov.) 1948.

The pathologic process is one of basilar meningitis. This may be the only evidence of neurosyphilis. There may be limitation of visual fields before atrophy of nerve fibers has occurred. At the clinic for treatment of ocular syphilis at Wills Hospital in Philadelphia, these investigators collected data on 397 patients with syphilitic primary optic atrophy. Of this number 20 had congenital syphilis. Of the 377 patients with acquired syphilis, 216 were white and 161 were Negro. Sixty-four per cent had a tabetic form of neurosyphilis; 30.5 per cent had diffuse meningovascular neurosyphilis; 2 per cent had the tabetic form of dementia paralytica, and 3.5 per cent had dementia paralytica. Of the 20 patients with congenital syphilis, 12 were white and 8 were Negro. Of this group 55 per cent had the tabetic form of neurosyphilis; 25 per cent, diffuse meningovascular neurosyphilis; 15 per cent, the tabetic form of dementia paralytica, and 5 per cent, dementia paralytica. The predominating age group in which patients with acquired syphilis complained of impaired vision was from 40 to 50. Males of both races were more affected than females, in a ratio of 3.5 to 1. In the series with congenital syphilis, females predominated. Altogether, optic atrophy was observed in patients ranging in ages from 9 to 75. Of the 377 patients with acquired syphilis, 309 (82 per cent) were untreated in the interval between the onset of loss of vision and their admission to the clinic. The remaining 68 patients (18 per cent) received treatment during this interval but previous to admission to the clinic. The majority of the 377 patients had received no treatment in the early stages of the infection, and few, if any, received treatment in amounts considered adequate according to modern standards. In addition to impaired vision as a symptom of optic atrophy, pain in the legs, diplopia, impairment of adaptation to light and difficulty in distinguishing colors may aid in an early diagnosis. The authors believe that the earliest symptoms of optic atrophy, preceding loss of central vision and pallor of the disk, is a visual field defect. The earliest field losses in primary optic atrophy are those of color, particularly red and green. Subsequent to development of the visual field defect, the optic disk shows some degree of pallor. Sixty-one per cent of the patients when first seen at the clinic were either industrially blind or had visual acuity of less than 1/60. To facilitate an early diagnosis it is necessary that ophthalmologists and physicians who examine patients with syphilis have a high degree of awareness of the optic nerve. The authors estimate that 90 per cent of blindness caused by syphilis can be attributed to optic nerve atrophy of acquired and congenital syphilis.

Bruetsch [154] believes that "the only close similarity between tabes and tabetic optic atrophy is the chronic syphilitic inflammation, which

154. Bruetsch, W. L.: What is the Relationship of So-Called Tabetic Optic Atrophy to Tabes Dorsalis? Tr. Am. Neurol. A. **73**:197-199, 1948.

produces the degeneration of the nerve fibers. In optic atrophy the inflammatory process is mainly located in the short segment of the intracranial portion of the optic nerves and in the chiasm. In tabes a similar inflammatory process is localized in the posterior roots and in the meninges of the spinal cord." He suggests that the term "tabetic optic atrophy" be discarded in favor of "syphilitic primary optic atrophy" because it may occur independent of tabes dorsalis.

NEUROSYPHILIS

Paroxysmal Hypertension Associated with Tabes Dorsalis.—The syndrome of paroxysmal hypertension is characterized by sudden and spontaneous rises in arterial blood pressure; between paroxysms the pressure is normal or slightly elevated. The episodes of hypertension may or may not be associated with symptoms. The syndrome of paroxysmal hypertension to some physicians is synonymous with pheochromocytoma, but there are other conditions which may be associated with this wide variation in arterial pressure, e. g., eclampsia, lead colic, abdominal angina of Nothnagel, cerebral tumor and tabes dorsalis. The occurrence of paroxysmal hypertension in patients with tabes dorsalis has received little attention in the literature since 1911. Bennett and Heyman [155] report 3 cases of paroxysmal hypertension associated with tabes dorsalis and stress this association, not only in the management of tabes dorsalis but to avoid unnecessary surgical exploration of the adrenal glands. In the first case the association was not recognized, and the patient was subjected to a needless surgical exploration for a pheochromocytoma. In this patient gastric crises, unaccompanied with pain, were associated with the episodes of hypertension. In the second case the hypertension was entirely asymptomatic. In the third case the paroxysms of hypertension were symptomless except for occasional association with lightning pains. After treatment with penicillin there was some beneficial effect in the first patient, but there was no evidence that the antibiotic was effective in the other 2 patients. The authors were unable to precipitate hypertension in these patients by the histamine and cold pressor tests. However, the first patient had gastric crises following the use of a laxative. Paroxysmal hypertension occurs in tabes dorsalis with or without symptoms and is believed to be an indication of a disturbance in the autonomic nervous system.

Pallhypesthesia.—Goldblatt [156] reports results of clinical investigation on the levels of pallesthesia on 200 patients taken from dermatologic

155. Bennett, I. L., and Heyman, A.: Paroxysmal Hypertension Associated with Tabes Dorsalis, Am. J. Med. **5**:729-735 (Nov.) 1948.

156. Goldblatt, S.: Pallhypesthesia: Depression of the Appreciation of Vibration in Trauma and in Disease, Arch. Neurol. & Psychiat. **59**:292-301 (March) 1948.

and venereal disease wards in an army hospital in England. The instrument employed in these tests was the Roth neurometer, which is a modified tuning fork designed to quantitate accurate levels of pallesthesia. The instrument delivers 70 decibels of energy at 128 double vibrations per second with a standard decaying time. A thin metal rod is inserted through the stem of the fork to act as a crossbar for the suspension of the instrument from the fingers. In mensuration the stem of the neurometer is used in the regular manner for sites other than the fingers. The technic of testing is described. Several tests were performed on each patient to compensate for a possible lack of objective method of testing and to verify response. Investigations were carried out on the fingers, great toe, tibia, malleolus, iliac crest, elbow and mastoid process and for hearing. A concealed stopwatch was used to determine the duration of vibration perceived by the patient. It was found that conditions producing general impairment of vibratory appreciation determined for the fingers were generally constant for the rest of the body. With conditions in which local neurologic lesions were suspected or proved, a wide divergence was noted in the values at various sites. The group of patients tested consisted of white persons and Negroes of both sexes. Ages varied from 18 to 45 years. Various types of cutaneous and venereal diseases were represented. However, chancroid and granuloma inguinale were not observed. So far as syphilis is concerned, in early infections, latent and late active phases, there were severe depressions of pallesthesia in almost all instances. Pallhypesthesia was noted when the primary lesion was less than one week old and in patients whose syphilis had apparently been completely quiescent for from twelve to twenty years after treatment. No abnormalities of position sense were noted in these patients. Depressions of vibratory appreciation were found in cases of asymptomatic as well as symptomatic neurosyphilis. In asymptomatic neurosyphilis position sense was intact. Diminution of vibratory appreciation remained constant on daily testing prior to treatment, and withdrawal of 5 cc. of spinal fluid produced no significant changes. A sharp fluctuation in vibratory appreciation occurred in some patients treated with penicillin (40,000 units every three hours for a total of sixty doses) which might be interpreted as a Herxheimer reaction. This deviation was followed by a gradual rise in the level of pallesthesia which did not at any time attain a normal rating, however.

GENERAL THERAPY

The therapy of syphilis has received more attention during the period covered by this report than has any other phase of this disease. On the whole, one may conclude that penicillin still holds the forefront,

but the numerous studies involving a variety of modifications of penicillin preparations and dosages attest to the as yet unsettled status of penicillin therapy of syphilis. The arsenicals and heavy metals have still some place in the research activities of some syphilologists. The following two papers are concerned with some of the factors modifying the outcome of treatment for syphilis.

Bauer and Price[157] made a statistical study on the influence of race, sex and stage of syphilis on the reported results of therapy. The material for this evaluation was records from two rapid treatment centers with the greatest volume of cases and the highest percentage of post-treatment observations. The study includes 6,310 patients with previously untreated primary and secondary syphilis and with post-treatment observations at the twelfth month on 75 per cent of the patients. The results of therapy were based on a total of all schedules (eight) and were measured by the cumulative percentage of retreated patients, including those with reinfection, clinical relapse, serorelapse or resistance, through twenty-four months following treatment. In comparing the results by the stage of syphilis, the retreatment rate among the white male with secondary syphilis is more than double the rates for patients treated for either seronegative or seropositive primary syphilis from the eighth through the twenty-fourth month. In the Negro males no significant differences in results of treatment are found among the stages of syphilis. In both seronegative and seropositive primary syphilis the cumulative retreatment rate for Negro males is about double the cumulative rate for white males from the seventh through the twenty-fourth month of post-treatment observations. No significant differences were observed among the four race-sex groups in patients treated for secondary syphilis. Thus it was demonstrated that the Negro males have a higher retreatment rate in the two primary stages of the disease, but in the secondary stage the rates for Negro and for white males are more in harmony. A logical explanation for the difference would be the greater number of reinfections in the Negro because of the higher incidence of syphilis in the Negro race. The bulk of the "retreatments" in the Negro race would actually represent reinfections rather than treatment failures. In secondary syphilis reinfections play a much less important role, as evidenced by the similarity of rates for white and for Negro males. For these reasons it is felt that the secondary stages of the disease furnish the best basis for the evaluation of treatment schedules. Analyses of variance by schedule of therapy were also made. In the first analysis, comparing the retreatment rates of primary and secondary syphilis for white

157. Bauer, T. J., and Price, E. V.: Results of Therapy by Race, Sex and Stage of Syphilis, J. Ven. Dis. Inform. **30**:1-7 (Jan.) 1949.

males, eight of the twelve schedules (600,000 to 10,000,000 units of penicillin) were included. The stage of syphilis at the time treatment is administered to white male patients is a definite factor in the results obtained. A second analysis is based on cumulative retreatment rates for Negro males by stage of syphilis, and eleven schedules are included. No significant difference is found among the stages of syphilis. A third analysis includes both seronegative and seropositive syphilis and compares the results of therapy in white and in Negro males. This analysis substantiates the observation that in primary syphilis Negro males have a higher retreatment rate than white males. A fourth analysis based on the cumulative retreatment rates for secondary syphilis includes all four race-sex groups and eight schedules of therapy. No significant difference in results of therapy exists between races and sexes in the secondary stage of syphilis. The authors note that one difficulty encountered in evaluation of this type is the uneven distribution of the race-sex group in the various stages of syphilis. Among the 6,310 patients there were only 11 white females with seronegative primary syphilis. The total patients were rather evenly divided between male (54 per cent) and female (46 per cent); however, they were predominantly Negroes (80 per cent) and persons with secondary syphilis (66 per cent).

In order to evaluate the intensive arsenical treatment of syphilis and later the penicillin therapy, many experimental studies were made by Iskrant, Bowman and Donohue,[168] statisticians of the Venereal Disease Division of the United States Public Health Service, and numerous variables were encountered. To evaluate the data properly and draw valid conclusions, special methods of statistical handling were devised to determine the actual value of the various systems of therapy. Before any two schemes of therapy are compared, the authors state, it is essential to examine the statistical methods used in order to determine whether apparent differences are due to the various statistical technics or to the efficacy of the treatment schedule. This paper presents in detail the methods used by the Venereal Disease Division. In addition it discusses statistical procedures used in other methods. Eight methods of analysis have been used by various investigators, and an actual group of 142 patients were subjected to statistical analysis by each of these methods. As each method is developed the results are discussed. It was observed that, depending on the method used, the percentage of patients whose serologic reactions became negative varied from 32 to 90 per cent in a twenty-two to twenty-four month period.

158. Iskrant, A. P.; Bowman, R. W., and Donohue, J. F.: Techniques in Evaluation of Rapid Antisyphilitic Therapy, Pub. Health Rep. **63**:965-977 (July 23) 1948.

Another example of gross differences obtained by the various statistical methods was the cumulative percentage of patients retreated. This varied from 26 to 61 per cent for the same time period. Hence it becomes evident that the methods employed in a statistical analysis are extremely important. Other obstacles to overcome are differences in criteria, as for example, of reinfection and relapse. Method 1 is the one used by the Venereal Disease Division for the evaluation of cases following treatment for syphilis. This method could be used in any other statistical analysis of other diseases also. This method was designed to make adjustments for the progressive loss of patients and continuous addition of new patients to the series. Method 2 is the life table method. It is similar to method 1 but adjusts for lapses by a different mathematical technic. The main difference in this method is that it cumulates the sustained seronegativity rates. Methods 3 to 8 apparently are inadequate and may mislead the casual observer as to results obtained in any treatment schedule. Anyone who has made a statistical study on large numbers of cases of early syphilis will appreciate a discussion of this type, since we ourselves have encountered innumerable variables in our work. Various methods of analysis were attempted with a good variation in results depending on the method used. However, we believe that the life table method corrected for many of these variables has yielded the most uniform and consistent results. Furthermore, it is accepted by statisticians. This article will be of extreme value to anyone undertaking a statistical analysis. It should be read and reread in the original form by anyone presenting data on evaluation of the therapeutic agent or anyone wishing to understand thoroughly and compare already published reports of drug evaluation.

Résumés of Treatment of Syphilis.—During this review period a series of résumés of the present treatment of syphilis have appeared. One may note from the following discussion of some of these how variable the therapeutic recommendations are.

Lynch [159] reviews briefly the current methods of treating syphilis. Details of his dosages are given as a sample of good practice in an urban community. Therapeutic agents which may be used include bismuth subsalicylate in oil, arsenic in the form of one of the phenarsine preparations, penicillin by the intramuscular route and fever by malaria or artificially. For early syphilis he recommends penicillin in a total dosage of 3,400,000 units in aqueous solution or 4,500,000 units of a mixture which allows slow absorption given over a period of seven to fifteen days. Concurrent administration of bismuth and arsenic preparations is advised. In visceral and cardiovascular syphilis, treatment should be

159. Lynch, F. W.: Current Views on the Treatment of Syphilis, Chicago M. Soc. Bull. **51**:206-209 (Sept. 25) 1948.

individualized. In order to avoid Herxheimer reactions, a series of injections of bismuth should be given before the administration of arsenic or penicillin. In neurosyphilis, the dose of penicillin should be 5,400,000 to 9,000,000 units. Bismuth and arsenic should be given over prolonged periods. Fever therapy is the preferred adjuvant to penicillin in parenchymatous neurosyphilis and in asymptomatic, meningeal and vascular processes which have failed to respond to bismuth and arsenic. In syphilis during pregnancy, a dose of penicillin of 2,400,000 units in aqueous solution or 4,800,000 units in slow-absorbing forms usually prevents congenital syphilis. Treatment of early congenital syphilis includes penicillin in a total dosage of 100,000 to 400,000 units per kilogram of body weight given in aqueous solution intramuscularly over a period of twelve to fifteen days. The addition of bismuth and sulfarsphenamine therapy for three to six months is valuable.

Brockman,[160] in his review of the treatment of syphilis, includes among the accepted therapeutic agents the heavy metals (bismuth subsalicylate preferred), the arsenicals (oxophenarsine hydrochloride and dichlorophenarsine hydrochloride preferred), penicillin and malaria.

A review of the various penicillin preparations, treatment schedules, results of therapy, treatment reactions and adjuvant medications, as recommended by the most prominent American syphilologists, are briefly discussed by Archambault,[161] of the Province of Quebec, Canada.

Thomas[162] has outlined in detail the recent development in the treatment of syphilis. This article should be read in the original, but Thomas points out the following facts: Penicillin therapy is the treatment of choice in all stages and types of syphilis. Early syphilis treated with 300,000 to 600,000 units of penicillin in oil and wax for fifteen days gives best results. Procaine penicillin G in oil with 2 per cent aluminum monostearate can be substituted for penicillin in oil and wax. Probably two weekly injections of 600,000 units for two to three weeks will do as much as 300,000 units of penicillin in oil and wax for three weeks. Neurosyphilis should be treated with 600,000 units of penicillin over a period of not less than fifteen days. Probably fewer injections with the newer repository products will give comparable results. Late symptomatic and late latent syphilis should be treated with 4,000,000 to 6,000,000 units given in not less than fifteen days. It may be impossible to reverse serologic reactions in cases of late syphilis much before five years, if then.

160. Brockman, G.: The Treatment of Syphilis, Kentucky M. J. **46**:263-269 (July) 1948.

161. Archambault, J.: Present Knowledge on the Use of Penicillin in the Treatment of Syphilis, Union méd. du Canada **77**:1215-1223 (Oct.) 1948.

162. Thomas, E. W.: Recent Developments in the Treatment of Syphilis, Am. J. Pub. Health **38**:1361-1369 (Oct.) 1948.

ARSENICALS

The next few papers are indicative of the waning interest in arsenical treatment of syphilis. These preparations are, however, generally considered valuable adjuncts to treatment with penicillin. There are scattered references to this fact in the discussion of some of the topics in this review. In many instances the continued use of arsenicals and heavy metals may be a matter of expediency or preference. For example, the World Health Organization Secretariat [163] submitted a summary of data from seventy-one countries showing the very limited production of penicillin and the worldwide need for it. On the basis of this and other evidence, the Expert Committee on Venereal Infections was convinced that the limited availability of penicillin is the chief restricting factor in venereal disease control in the world today. It was suggested that the World Health Organization might well assume responsibility for the promotion of those processes which promise to increase the production and availability of penicillin.

On the other hand, Hellerström and Hagerman [164] feel that penicillin in the most frequently used dosage (2,400,000 units given in sixty injections during seven and one-half days) is markedly inferior in action to the conventional treatment with arsphenamine and bismuth, especially in the later stages of syphilis, in which they report a 15 to 20 per cent relapse, serologic or clinical. In the Scandinavian countries, where the supply of penicillin is limited, these authors feel that penicillin is the preferable treatment only in certain types of cases, such as (1) cases of congenital syphilis in infants and young children, (2) cases of recently diagnosed syphilis in pregnant women, (3) cases of intolerance to arsenicals and/or bismuth, (4) cases of resistance to arsenicals and/or bismuth and (5) certain cases of neurosyphilis, especially if there is any contraindication to fever therapy.

In addition, Lapière [165] concludes that the combination of neoarsphenamine and an oil-soluble bismuth preparation employed in a five month schedule, remains the most efficient means of treating syphilis.

With the same tone, Degos,[166] in discussing the treatment of early syphilis, recommends the use of penicillin because of its rapid action on the disappearance of the treponeme, but urges that several courses of an oil-soluble bismuth preparation should follow.

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163. Penicillin in Venereal Diseases, Chron. World Health Organ. **3**:15-16 (Jan.) 1949.

164. Hellerström, S., and Hagerman, G.: Penicillin in Venereology, Acta dermat.-venereol. **28**:81-94, 1948.

165. Lapière, S.: Notre plus récente expérience dans le traitement de la syphilis, Rev. méd. Liège **3**:513-517 (Sept. 15) 1948.

166. Degos, R.: Le traitement d'attaque de la syphilis recente, Semaine d. hôp. Paris **25**:651-654 (Feb. 26) 1949.

Binding of Arsenicals by Red Blood Cells of Rabbits.—Fink and Wright [167] review the literature and present a report of studies in which the extent of the adsorption of oxophenarsine on the red blood cells of the rabbit was determined, followed by an investigation of its degree of reversibility. The investigations showed that through the oxophenarsine concentration range of from 1:1,000 to 1:500,000, from 28 to 85 per cent of the oxophenarsine added to heparinized rabbit blood was bound by the red cells in one-half, four or eight hours. The oxophenarsine bound by the cells increased with increasing concentration of the drug to a maximum of 85 per cent at the concentration of 1:5,000. Adsorption played the major role in the binding of oxophenarsine within the concentration range of 1:5,000 to 1:100,000, as evidenced by substantial adherence to the Freundlich adsorption isotherm equation. Even at the highest concentration of oxophenarsine used, the surface of the red blood cells showed little evidence of being saturated. The adsorption of oxophenarsine on the rabbit's red blood cell was not completely reversible when the oxophenarsine-containing cells were resuspended three times in fresh plasma, although the per cent of the drug not liberated by the cells decreased progressively after each resuspension. The degree of reversibility of the reaction was in most cases greater than 60 per cent for the first resuspension and in the case of the lowest concentration used approached as high as 90 per cent. This suggests that factors other than simple adsorption probably enter into the binding of oxophenarsine by the red cells.

In another paper, the same authors [168] refer to previous experiments in which it was demonstrated that the adsorption of oxophenarsine on erythrocytes was not completely reversible, and present a report of investigations of the role played by various factors other than adsorption on the cell surface. The ability of oxophenarsine to dialyze from a blood suspension was determined both in the presence of the intact cell membrane (normal erythrocytes) and after complete removal of the cell membrane (laked blood). Preliminary experiments indicated that oxophenarsine is 95 per cent dialyzable through a collodion membrane from modified dextrose Ringer's solution, serum and serum containing saponin. It was further demonstrated that of the 48 per cent of oxophenarsine that dialyzed from defibrinated blood, 20 per cent

167. Fink, L. D., and Wright, H. N.: An Investigation of the Nature and Extent of the Binding of Oxophenarsine (Mapharsen) by the Red Blood Cell of the Rabbit in Vitro: I. Adsorption on the Cell Surface, J. Pharmacol. & Exper. Therap. **94**:455-464 (Dec.) 1948.

168. Fink, L. D., and Wright, H. N.: An Investigation of the Nature and Extent of the Binding of Oxophenarsine (Mapharsen) by the Red Blood Cell of the Rabbit in Vitro: II. Factors Other Than Adsorption, J. Pharmacol. & Therap. **94**:465-471 (Dec.) 1948.

represented the amount present in the serum and 28 per cent was the oxophenarsine reversibly bound to the cell surface. An additional 27 per cent of oxophenarsine dialyzed when the intact cell membrane was destroyed with saponin. The hemoglobin accounted for 13 per cent of the oxophenarsine bound by the laked defibrinated blood. The extent of binding by the stroma was only slight and not sufficiently different from that of serum that one could be sure that the numerical differences represented a statistically significant difference. The role of the free sulfhydryl groups of proteins in the binding of oxophenarsine was further substantiated by demonstrating the lack of binding of oxophenarsine by serum, its moderate binding by hemoglobin and its extensive binding by urease.

HEAVY METALS

Willcox [169] is of the opinion that bismuth still has a place in syphilotherapy. In late syphilis its use may prevent therapeutic shock and therapeutic paradox, especially in the presence of such conditions as aortitis with involvement of the coronary ostia, gumma of the larynx, optic atrophy, syphilitic meningitis and gumma of the liver. In such cases risks may be lessened by bismuth given for four to eight weeks before penicillin or arsenical therapy. Willcox states that some authorities (particularly the French) still recommend additional short courses of bismuth and/or an arsenical. In congenital syphilis, early or late, treated with penicillin, many employ two full ten week courses of sulfarsphenamine and bismuth. The preparation of choice used in England is aqueous suspensions of bismuth metal or bismuth oxychloride in a 10 to 20 per cent suspension containing an equivalent of 0.08 to 0.16 Gm. of bismuth metal respectively. The dose is 2 cc. of a 10 per cent suspension or 1 cc. of a 20 per cent suspension given intramuscularly once or twice weekly.

PENICILLIN

Pharmacology of Penicillin.—Mode of Action: Hotchkiss [170] reviews the mode of action of chemotherapeutic agents on various bacteria. While spirochetes were not studied, the principles may apply to these organisms. He states that the phenomena of antimicrobial action are observed at many levels. Frequently this action can be classified with some accuracy as either bacteriostatic or bactericidal (inhibitory to growth or lethal). However, at this point the complexity of biologic matters begins to make itself felt—it now appears that some agents may prevent or interfere with growth and, in so doing, initiate characteristic processes which lead

169. Willcox, R. R.: The Role of Bismuth Oxychloride in the Treatment of Syphilis, Practitioner **161**:203-204 (Sept.) 1948.

170. Hotchkiss, R. D.: The Mode of Action of Chemotherapeutic Agents, Ann. Rev. Microbiol. **2**:183-214, 1948.

to death of the organism. Since these lethal processes apparently do not occur if the environment is unsuitable for growth, the action is neither bacteriostatic nor bactericidal in the simple sense of those terms. Elucidation of the mechanism of antibacterial action is likely to require information at all the following levels: (*a*) the physical-chemical process by which the agent attains a toxic concentration on or within the affected cell (simple diffusion, adsorption, active absorption); (*b*) the interaction of the agent at this concentration with some morphologic element or with some metabolic constituent of the cell; (*c*) the interference with a normal cellular function occasioned by this interaction, and (*d*) the alteration, gradual or immediate, in the biochemical growth processes of the cell by virtue of this interference. For some time it has been realized that susceptible bacteria, if attempting to grow in the presence of penicillin, were rapidly rendered nonviable, whereas nonproliferating cultures remained viable and relatively unaffected. It is known that during inhibition of growth in penicillin bacteria often produced pleomorphic diphtheroids, filamentous or "swollen" forms. Gahe and Taylor report that staphylococci grown in a low concentration of penicillin have almost completely lost the ability to accumulate free glutamic acid inside the cell. There is thus some reason to think that a specific injury has been done to the cell during the growth in the presence of penicillin, and it seems reasonable to suppose that the resultant inability to use glutamic acid may prevent growth. It still remains a mystery why cells must be exposed to penicillin in a growth medium before an inhibitory effect develops. There is considerable evidence in the literature that sulfhydryl compounds can inactivate penicillin, and the suggestion has been made that penicillin can, by virtue of this interaction, inactivate biologically important sulfhydryl-containing enzymes. Another factor which in certain mediums and in vivo determines accessibility of penicillin to bacteria is the extent of binding of these agents by serum albumin.

According to Dufrenoy and Pratt,[171] in penicillin-sensitive organisms penicillin blocks the normal functioning of sulfhydryl groups. The blocking results from sulfhydryl groups of essential polypeptides of the glutathione type being dehydrogenated more rapidly than they are rehydrogenated. Exposure of the cells to bacteriostatic concentrations of penicillin results in "decompensated respiration," or a shift of the sulfhydryl (—SH) to disulfide (S—S), of aldehydic COH to carboxylic COOH or to ketonic CO, or enolic COH to ketonic CO. Concomitantly bacteria lose inherent properties as staining properties. The authors made a study of the distribution of phosphates, aldehydes and alkaline phosphatase activity on different parts of penicillin assay plates seeded with Staph. aureus and Bacillus subtilis. The molybdenic reagent and a

171. Dufrenoy, J., and Pratt, R.: Cytochemical Mechanism of Penicillin Action, J. Bact. **56**:99-105 (July) 1948.

modified Gömöri test were used to demonstrate the location of phosphates. Aldehydes were revealed by the use of Schiff reagent and use of azobenzenephenyl hydrazine sulfonic acid and sulfuric acid. Pretreatment of plates with a solution containing nitromethane in alcohol and aqueous potassium carbonate, which Genevois has shown blocks aldehyde groups, prevented development of a positive reaction with the aldehyde reagents. This is evidence that positive reactions obtained in the absence of pretreatment with the blocking agent were actually due to the presence of aldehydes. Sites of phosphatase activity were located by the use of triphenolphthalein phosphate followed by alkalinization. Positive reactions for phosphates, aldehydes and alkaline phosphatase activity were obtained throughout the uninhibited regions and were most intense at the sites of the ring of enhanced growth which surrounds each inhibition zone and which corresponds to a region in which cells are exposed to appreciable but subbacteriostatic concentrations of penicillin. Only negative reactions were obtained within the inhibition zones. Serial dilution studies with broth cultures confirmed the results obtained in assay plates.

Pratt and Dufrenoy [172] in a later paper noted that "the inhibition of enzyme systems involved in the transfer and in the diphosphorylation of complex ribonucleates is fundamentally involved in the action of penicillin on gram-positive organisms." This is substantiated by the experiments reported. Assay plates seeded with appropriate test organisms were either incubated overnight with penicillin or were preincubated for three hours without penicillin, then were incubated for three hours with penicillin. The plates were then treated first with an 0.1 per cent solution of triphenyltetrazolium chloride, then with an 0.1 per cent solution of trypan blue. The results demonstrate that (*a*) subbacteriostatic concentrations of penicillin or polymyxin induce an increase in reducing activity and in staining attributed to ribonucleic acid materials; (*b*) bacteriostatic concentrations suppress the reducing activity but permit the cells to retain maximal ability to absorb trypan blue, suggesting inhibition of the enzyme system responsible for the splitting of phosphoric acid away from the ribose fraction.

Werner and Kellenberger [173] utilized the electron microscope in their study of the mode of action of antibiotics. They observed the changes of B. subtilis when acted on by streptomycin. They described three stages of alteration: (1) appearance of cells of highly turgescent character, the cytoplasm of which is intimately applied against the cell wall; (2) extreme

172. Pratt, R., and Dufrenoy, J.: Cytochemical Mechanisms of Penicillin Action: Involvement of Ribonucleic Acid Derivatives, J. Bact. **57**:9-13 (Jan.) 1949.

173. Werner, G. H., and Kellenberger, E.: Le rôle du microscope électronique dans l'étude du mode d'action des antibiotiques, Bull. schweiz. Akad. d. med. Wissensch. **4**:263-274 (Nov.) 1948.

shrinkage of the cytoplasm inside the cellular envelope, and (3) extrusion of the cytoplasm from the cellular envelope, which remains empty and often presents interruptions.

Pratt, Dufrenoy and Sah[174] demonstrate that vitamin K and penicillin act synergistically, as the antibacterial activity of the two combined was greater than the sum of their individual activities.

Rate of Bactericidal Action: Eagle and Musselman,[175] in a well planned investigation, studied the effect of the concentrations of penicillin on the rate of the bactericidal action in vitro against a total of forty-one strains of alpha and beta hemolytic streptococci, Staph. aureus, Staph. albus, Diplococcus pneumoniae and the Reiter strain of T. pallidum. For every organism studied the authors could define a concentration at which the net rate of multiplication was significantly reduced, a somewhat higher concentration at which the organisms were killed faster than they multiplied, so that the net number of viable organisms slowly decreased, and, lastly, a maximally effective concentration at which the organisms died at a maximum rate which was not increased further even by a 32,000 fold increase in penicillin concentration. The several bacterial species were found to differ with respect to the magnitude of this maximally effective concentration of penicillin and also with respect to the maximal rate at which they could be killed by the drug; furthermore, there was no necessary relation between the two values. In addition, with many bacterial species there was a sharply defined concentration of penicillin at which it was optimally effective and in excess of which the number of organisms killed was paradoxically reduced rather than increased. Specifically with regard to the cultured Reiter strain of T. pallidum, their experiments showed that a concentration of 0.016 microgram per cubic centimeter decreased the net rate of multiplication; the minimal concentration with a net bactericidal action was 0.032 microgram per cubic centimeter, and almost maximum effect was produced by a concentration of 0.25 to 1 microgram per cubic centimeter. Thereafter, a 2,000 fold increase in penicillin (2,048 micrograms per cubic centimeter) only slightly accelerated the death rate of T. pallidum (Reiter's). The treponemal cultures were killed at a much slower rate than were cultures of Str. pyogenes. To kill 99.9 per cent of the treponemes at the maximal effective level of 1 microgram per cubic centimeter twenty-three to thirty-three hours was required against 1.4 to

174. Pratt, R.; Dufrenoy, J., and Sah, P. P. T.: Enhancement of Penicillin Activity in Vitro by Vitamin K_5, J. Am. Pharm. A. (Scient. ed.) **37**:435-438 (Oct.) 1948.

175. Eagle, H., and Musselman, A. D.: The Rate of Bactericidal Action of Penicillin in Vitro as a Function of Its Concentration, and Its Paradoxically Reduced Activity at High Concentrations Against Certain Organisms, J. Exper. Med. **88**:99-131 (July 1) 1948.

2.2 hours for the streptococci, and the proportion of treponemens surviving after six hours was 1 to 10 per cent, as compared with 0.002 to 0.01 per cent for the streptococci. The foregoing discussion involves the several factors of effective penicillin concentration, the varying rates at which different bacterial strains can be killed and the total length of time for which the bacteria were exposed to the effective concentrations. A corollary to this discussion is the therapeutic problem as to whether the exposure to penicillin should be continuous, and the penicillin concentrations in vivo therefore sustained at the effective bactericidal levels, or whether the levels may be intermittently allowed to fall below those effective levels without prejudicing the outcome of treatment. Eagle suggests that in infections caused by the zone-sensitive bacteria a number of relatively small doses of penicillin repeated at appropriate intervals, or the slowly absorbed penicillin in oil and beeswax, may be more effective therapeutically than extremely large injections which maintain the tissue concentration at excessively high levels. In such infections it may be well to give a continuous infusion at a rate designed to maintain at the focus of infection a concentration of penicillin approximating that which is maximally effective for the particular organism.

Absorption-Delaying Vehicles: To the many absorption-delaying vehicles for penicillin now under investigation, Buckwalter and Dickison [176] propose peanut oil–aluminum stearate gels as repository forms superior to peanut oil alone or peanut oil–beeswax combination. Ercoli and his co-workers,[177] in studies made on dogs and on human subjects, found that epinephrine-oil preparations were effective in prolonging blood levels. Pardo and his colleagues [178] found pectins in proper concentration suitable for slowing absorption of penicillin.

The possible enhancement of the penetration of penicillin into a mucous membrane by hyaluronidase was investigated by Som, Schneierson and Sussman [179] in 26 patients with chronic suppurative disease of the maxillary sinus and in 5 subjects clinically free from sinus disease. It is possible that the combination of parenterally administered penicillin and hyaluronidase in syphilotherapy may be worth while. The authors state that it may be concluded that the higher blood levels following

176. Buckwalter, F. H., and Dickison, H. L.: A New Absorption Delaying Vehicle for Penicillin, J. Am. Pharm. A. **37**:472-474 (Nov.) 1948.

177. Ercoli, N.; Hueper, W. C.; Landis, L.; Schwartz, B. S., and Queally, F. J.: A New Vehicle for Parenteral Reposition Therapy, J. A. M. A. **138**:115-117 (Sept. 11) 1948.

178. Pardo, C. C.; Langer, A.; Baquero, G. F.; Ballina, R. P., and Piñeyro, R.: Un neuvo disolvente para la absorcion prolongada de la penicillina, Bol. Soc. cubana dermat. y sif. **5**:5-14 (March) 1948.

179. Som, M. L.; Schneierson, S. S., and Sussman, M. L.: Enhancement of Penetration of Penicillin into Inflamed and Normal Mucous Membrane by Hyaluronidase, Proc. Soc. Exper. Biol. & Med. **70**:96-99 (Jan.) 1949.

hyaluronidase are due to greater diffusion and penetration of the penicillin as a result of the spreading action of hyaluronidase.

Blood Levels: Ercoli and his associates [180] made studies in rats on the relationship between duration of therapeutic effectiveness and the penicillin blood level as determined by in vitro methods. Rats were given intramuscular injections of a preparation containing crystalline potassium penicillin G, peanut oil and epinephrine. Blood levels were determined at various intervals. Groups of previously treated animals were inoculated with a serum-broth culture of streptococci or penumococci. Detectable blood levels were present in 90 per cent of the animals for fourteen to eighteen hours. In the pneumococcic infections a protective effect was evident six to eight hours after a penicillin blood level was no longer detectable. Of rats infected twenty hours after treatment, two hours after disappearance of penicillin from the blood, 42 per cent were cured (survived for three weeks), and death was delayed in 62 per cent. Control animals died in two to three days. In the hemolytic streptococcus infections, chemotherapeutic effectiveness of penicillin appeared to be present for four to eight hours after penicillin blood levels were not detectable. Ten of 30 rats infected two to six hours after disappearance of penicillin from the blood survived for twenty-one days, whereas 75 per cent of 20 controls died in two days. The authors state that these findings only partly explain the opinion of some investigators that continuous penicillin blood levels are unnecessary. Other factors accounting for a penicillin effect independent of the blood level are the additive effect of repeated doses of penicillin, the accumulation of penicillin in the tissues and the immunologic response of the host.

Eagle and his co-workers [181] studied the serum levels of penicillin G following intramuscular injections of aqueous preparations into men, rabbits and mice. The method of assay was the serial dilution technic. Blood levels were taken after one-fourth, one-half, one, two, three and four hours. After the initial period of rapid absorption the blood levels fell off rapidly. In men the percentage drop per hour over the first two hours varied from 65 at the higher dosages to 80 in the smaller dosage range. In rabbits there was a 65 per cent decrease each hour. In mice, however, the blood levels during the first two hours fell to 91 to 99 per cent per hour. At the largest dosage (200 mg. per kilogram) a slower rate developed after several hours. The serum concentrations for a given

180. Ercoli, N.; Lewis, M. N.; Schwartz, B. S., and Whitehead, M.: Fate and Distribution of Penicillin in the Body: II. Duration of Blood Concentration and Chemotherapeutic Effectiveness, Proc. Soc. Exper. Biol. & Med. **69**:297-299 (Nov.) 1948.

181. Eagle, H.; Fleischman, R., and Musselman, A. D.: The Serum Concentration of Penicillin G in Mice, Rabbits and Men After Its Intramuscular Injection in Aqueous Solution, J. Bact. **57**:119-126 (Jan.) 1949.

dose of penicillin in men were three to five times higher than in rabbits. The levels in rabbits and mice began at the same concentrations but rapidly diverged because of faster disappearance in mice. Bactericidal levels were sustained 50 per cent longer in man than in rabbits, probably owing to the higher concentration achieved in human serum. In turn, the therapeutic levels were approximately three times higher in rabbits than in mice. For equal doses of penicillin the serum levels at a given time were highest in men, next highest in rabbits and lowest in mice, in a ratio of 4½ : 3 : 1 respectively. The initial level in men was three to five times greater than it was in mice or rabbits and indicative of a significant species difference in the initial distribution of the drug in body fluids. Penicillin disappeared at the rate of 65 per cent an hour in rabbits and 91 to 99 per cent an hour in mice. To prolong a given serum level by one hour would require approximately a twofold increase in dosage in man, a threefold increase in rabbits and a five to twentyfold increase in mice.

(To Be Concluded)

News and Comment

GENERAL NEWS

American Heart Association Makes Research Awards.—The American Heart Association has made research awards totaling $140,000 to thirty-four investigators. Two of the scientists, Dr. Edward H. Bloch, of Chicago, and Dr. John P. Merrill, of Boston, received five year grants for independent research; the remaining thirty-two will be research fellows chosen on a one year basis.

Postgraduate Courses.—The following postgraduate courses have been arranged by the American College of Physicians: 1. Clinical Allergy, Feb. 6-17, 1950; Robert A. Cooke, M.D., F.A.C.P., director; Roosevelt Hospital, New York; fees, $120 for members of the American College of Physicians and $240 for nonmembers. 2. Diseases of the Blood Vessels, March 13-18; Irving S. Wright, M.D., F.A.C.P., Director; Cornell University Medical College, New York; fees, $30 for members of the American College of Physicians and $60 for nonmembers. 3. Recent Developments in the Cardiovascular Field, March 20-25; Louis N. Katz, M.D., F.A.C.P., director; Michael Reese Hospital, Chicago; fees, $30 for members of American College of Physicians and $60 for nonmembers. 4. Electrocardiography: Basic Principles and Interpretation, May 8-13; Conger Williams, M.D., director; Massachusetts General Hospital, Boston; fees, $60 for members of the American College of Physicians and $120 for nonmembers. 5. Endocrinology, May 15-20; Willard O. Thompson, M.D., F.A.C.P., director; University of Illinois College of Medicine, Chicago; fees, $30 for members of the American College of Physicians and $60 for nonmembers. 6. The Dynamics of Metabolic Diseases, May 15-20; Clarence E. de la Chapelle, M.D., F.A.C.P., director; New York University Post-Graduate Medical School, New York; fees, $30 for members of the American College of Physicians and $60 for nonmembers. 7. Trends and Newer Developments in Internal Medicine, June 5-10; Thomas M. Durant, M.D., F.A.C.P., director; Temple University School of Medicine, Philadelphia; fees, $30 for members of the American College of Physicians and $60 for nonmembers. 8. Internal Medicine, June 19-23; Stacy R. Mettier, M.D., F.A.C.P., director; University of California Medical School, San Francisco; fees, $30 for members of the American College of Physicians and $60 for nonmembers. 9. Clinical Aspects of Malnutrition, August 14-26; Salvador Zubiran, M.D., F.A.C.P., director; Hospital de Enfermedades de la Nutricion, México, D.F., Mexico; fees, $60 for members of the American College of Physicians and $120 for nonmembers.

NOTE

Attention of the readers is called to the fact that the April issue will contain as a special feature the first full and comprehensive report of the original work on ACTH and cortisone by Philip S. Hench and collaborators at the Mayo Clinic, as well as a complete review of all pertinent experimentation to date on these and allied substances. Extra copies will be available.

Book Reviews

Textbook of Medicine. Ninth edition. By various authors. Price, $8.00. Pp. 875, with 28 illustrations. Williams & Wilkins Company, Mount Royal and Guilford aves., Baltimore 2, 1949.

Sir John Conybeare and his associates, in the main of Guy's Hospital, London, have revised their classic textbook extensively. The ninth edition appears in a new format and is a concise and readable summary of the field of internal medicine; it differs from similar but somewhat more extensive American texts in that some space is allotted also to diseases of infants and to dermatology. The book is characterized by its emphasis on diagnosis by clinical study, with only minimal discussions of highly technical laboratory procedures, and by its relative brevity. It contains 856 pages of easily legible single column type. These features make it a convenient point of departure for students who often tend to get lost when introduced to clinical medicine by our more comprehensive American texts, and American practitioners will find it a stimulating and refreshing summary of the medical views of our British colleagues. Because the book is intended as a textbook and not as a reference, controversial points are avoided and documentation omitted.

Malaria—The Biography of a Killer. By Leon J. Warshaw. Price, $3.75. Pp. 348. Rinehart & Co., Inc., 232 Madison Ave., New York, 1949.

The hobby reading of a cardiologist, together with the interest of a publisher patient, resulted in the publication in November 1949 of an entertaining book on the story of malaria. It is regrettable that such an excellent work not only fails to state the present situation of malaria in the United States but, by quoting old and unreliable statistics, suggests an incidence of millions instead of hundreds of cases today. This misconception has already been further propagated by the lay press.

Aside from the inaccuracy in the chapter on distribution just mentioned, the book carries a story of the workers in malaria and of the searches for new and better sources of quinine in a sound, yet dramatic manner. Many little-known historical facts are faithfully recorded. The following comments are noteworthy: 1. It would seem reasonable for a writer of such training to have separated more clearly Plasmodium falciparum infections from those due to Plasmodium vivax and quartan infections. 2. Few will agree with the statement that quartan malaria produces the highest fever, or with Dr. Warshaw's observations on the effect of the mosquitoes' salivary fluid. 3. Another weak point is the omission of the latest successful cultivation of the parasites in vitro. 4. The continuation of use of the term "malaria cachexia" is to be deplored.

On the other hand, how many physicians know that the full effect of malaria on the development of the country in its early days was extremely powerful, that Osler first considered the parasites in blood smears to be artefacts, that McCallum first recognized fertilization of gametocytes, that Ronald Ross was offered to New Orleans in the 1895 yellow fever epidemic, that the people of Philadelphia in 1793 were told to put whale oil in their rain barrels as a preventative of mosquito breeding, that an English charlatan, Tabor, and malaria caused Molière to ridicule current French medicine with his famous comedy of manners "La

malade imaginaire" in 1680 or that Peltier and Caventou isolated emetine, strychnine and bruceine in pure form as well as isolating quinine?

Because of its dramatic interest, the story of cinchona and quinine occupies a larger share of the book than its importance warrants, whereas in comparison the newer drugs, infinitely more important, have been slighted. The story of the part played by malaria in both world wars is interestingly told. The chapter on artificial malaria is perhaps a little too optimistic.

Dr. Warshaw's book is an entertaining and instructive story of malaria and can be readily followed by the layman as well as the physician. It is regrettable that such a book fails to state more clearly the current situation with regard to malaria in the United States.

Coagulation, Thrombosis and Dicumarol. By S. Shapiro, M.D., and M. Weiner, M.D. Price, $5.50. Pp. 131, with 11 illustrations. Brooklyn Medical Press, Inc., P. O. Box 99, Station H, New York 25, 1949.

This little monograph adequately covers the ground outlined in its title. Much of the material is, of course, to be found elsewhere, but it is convenient for those specially interested to have available this up-to-date and well documented review.

Clinical Examination of the Nervous System. By G. H. Monrad-Krohn, M.D. Ninth edition. Price, $5. Pp. 459, with 131 illustrations. Paul B. Hoeber, Inc., 49 E. 33rd St., New York 16, 1949.

This little book, now in its ninth edition, gives an excellent review of practical neurologic diagnosis along classic lines. It is well printed and illustrated but seems to the reviewer to add little to a number of recent monographs covering the same domain in perhaps more comprehensive fashion.

Secretory Mechanism of the Digestive Glands. By B. P. Babkin, M.D., D.Sc., Ll.D., F.R.S.C. Price, $20. Pp. 1,027 with 233 illustrations. Paul B. Hoeber, Inc., 49 E. 33rd St., New York 16, 1949

The second edition of this useful book is more comprehensive than the first. It contains discussions of some of the recent advances in the relation of psychologic states to gastroenterologic functions as well as many other isolated recent observations. The mechanism of glandular function is more extensively discussed, including a presentation of the humoral and neurogenic regulatory factors. The book is well written and is presented in the same general fashion as the first edition. The bibliography is extensive and is up to date. This monograph should prove to be useful to internists and gastroenterologists as well as students and is highly recommended to anyone interested in the function of the digestive glands.

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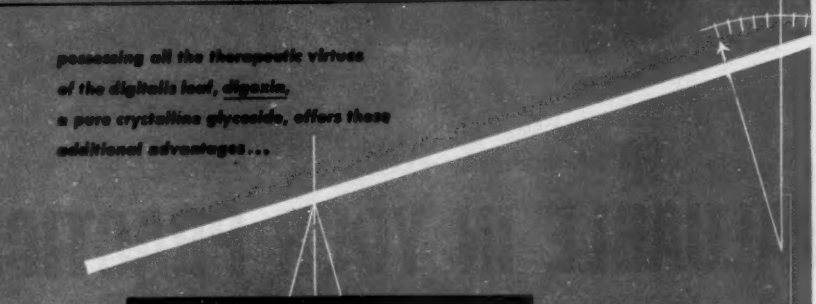

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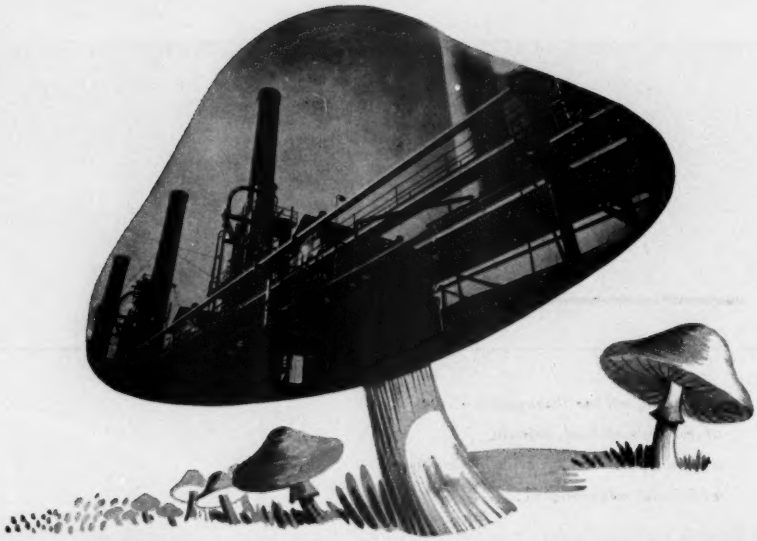

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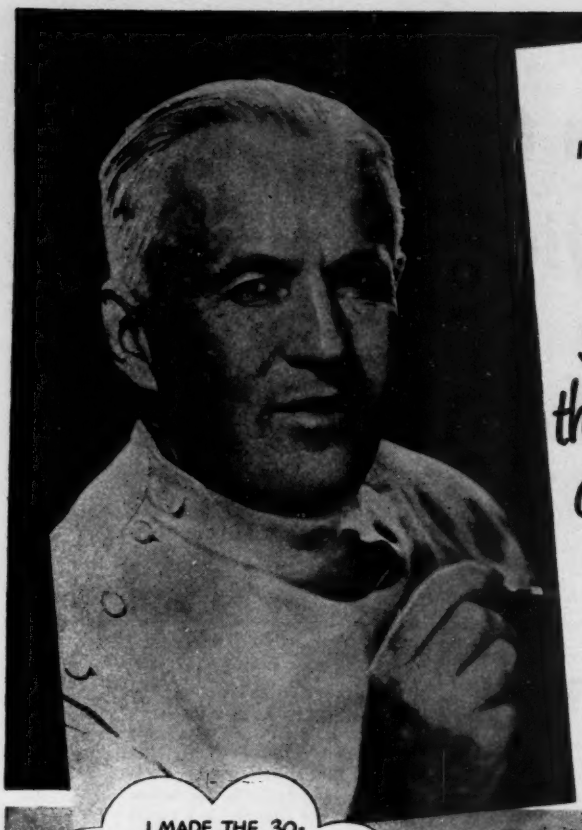

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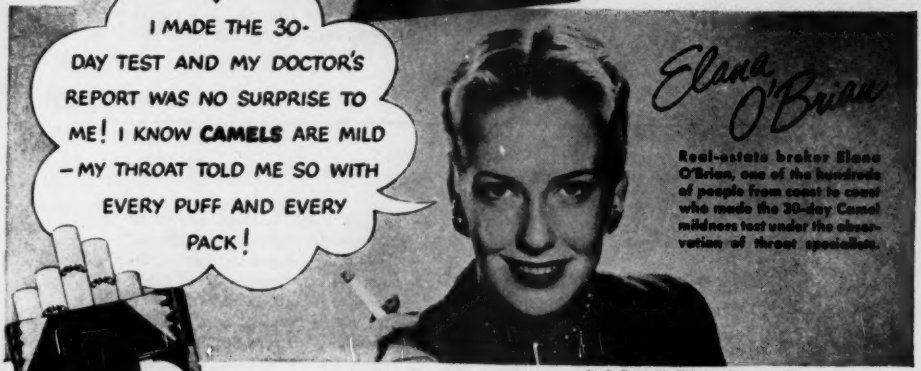
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